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(54) Title: CLONING BY COMPLEMENTATION AND RELATED PROCESSES

(57) Abstract

Disclosed are methods for detecting mammalian genes encoding proteins which can function in microorganisms, particularly yeast, to modify, complement, or suppress a genetic defect associated with an identifiable phenotypic alteration or characteristic in the microorganism. Disclosed also are mamalian DNA sequences cloned bythe above method, as well as polypeptide products of the expression of the DNA sequences in procaryotic or eucaryotic host cells and antibody substances which are specifically immunoreactive with said expression products. More specifically, the present invention methods for cloning mammalian genes which encode products which modify, complement or suppress a genetic defect in a biochemical pathway in which cAMP participates or in a biochemical pathway which is controlled, directly or indirectly, by an *RAS* protein, to products (RNA, proteins) encoded by the mammalian genes cloned in this manner, and to antibodies which can bind the encoded proteins.

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CLONING BY COMPLEMENTATION AND RELATED PROCESSES

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CROSS-REFERENCE TO RELATED PATENT APPLICATION

This application is a continuation-in-part of co-pending U.S. Serial No. 07/511,715; filed April 20, 1990.

BACKGROUND

The present invention relates generally to novel cloning methods, to the DNA sequences obtained using these methods, the corresponding expression products of the DNA sequences and antibodies thereto, as well as to novel screening methods for compounds affecting protein activity. More specifically, the present invention provides novel complementation screening methods particularly useful in the isolation of DNAs encoding cyclic nucleotide phosphodiesterase polypeptides (PDEs) and RAS-related proteins. These DNAs, in turn, provide valuable materials useful as hybridization probes for related DNAs and useful in obtaining polypeptide expression products when used to transform suitable host cells.

Of interest to the present invention are the following discussions relating to the cyclic nucleotide phosphodiesterases and RAS related proteins.

The RAS genes were first discovered as the transforming principles of the Harvey and Kirsten murine sarcoma viruses [Ellis *et al.*, *Nature*, 292:506 (1981)]. The cellular homologs of the oncogenes of Harvey and Kirsten murine sarcoma viruses (H-RAS and K-RAS) constitute two members of the RAS gene family [Shimizu *et al.*, *Proc. Natl. Acad. Sci.*, 80:2112

(1983)]. A third member is N-RAS [Shimizu et al., Proc. Natl. Acad. Sci., 80:2112 (1983)]. These genes are known as oncogenes since point mutations in RAS can result in genes capable of transforming non-cancerous cells into cancerous cells [Tabin et al., Nature, 300:143 (1982); Reddy et al., Nature, 300:149 (1982); Taparowsky et al., Nature, 300:762 (1982)]. Many tumor cells contain RAS genes with such mutations [Capon et al., Nature, 302:33 (1983); Capon et al., Nature, 304:507 (1983); Shimizu et al., Nature, 304:497 (1983); Taparowsky et al., Cell, 34:581 (1983); Taparowsky et al., Nature, 300:762 (1982); Barbacid, Ann. Rev. Biochem., 56:779 (1987)].

Despite the importance of the RAS oncogenes to our understanding of cancer, the function of RAS genes in mammals is not known. The RAS proteins are small proteins (21,000 daltons in mammals) which bind GTP and GDP [Papageorge et al., J. Virol., 44:509 (1982)]. The RAS proteins hydrolyze GTP slowly; specific cellular proteins can accelerate this process [McGrath et al., Nature, 310:644 (1984); Trahey et al., Science, 238:542 (1987)]. RAS proteins bind to the inner surface of the plasma membrane [Willingham et al., Cell, 19:1005 (1980)] and undergo a complex covalent modification at their carboxy termini [Hancock et al., Cell, 57:1167 (1989)]. The crystal structure of H-RAS is known [De Vos et al., Science, 239:888 (1988)].

The yeast Saccharomyces cerevisiae contains two genes, RAS1 and RAS2, that have structural and functional homology with mammalian RAS oncogenes [Powers et al., Cell, 36:607 (1984); Kataoka et al., Cell, 40:19 (1985); Defeo-Jones et al., Science, 228:179 (1985); Dhar et al., Nucl. Acids Res., 12:3611 (1984)]. Both RAS1 and RAS2 have been cloned from yeast plasmid libraries and the complete nucleotide sequence of their coding regions has been determined [Powers et al., Cell,

36:607 (1984); DeFeo-Jones et al., Nature, 306:707 (1983)]. The two genes encode proteins with nearly 90% identity to the first 80 amino acid positions of the mammalian RAS proteins, and nearly 50% identity to the next 80 amino acid positions. Yeast RAS1 and RAS2 proteins are more homologous to each other, with about 90% identity for the first 180 positions. After this, at nearly the same position that the mammalian RAS proteins begin to diverge from each other, the two yeast RAS proteins diverge radically. The yeast RAS proteins, like proteins encoded by the mammalian genes, terminate with the sequence cysAAX, where A is an aliphatic amino acid, and X is the terminal amino acid [Barbacid, Ann Rev. Biochem., 56:779 (1987)]. Monoclonal antibody directed against mammalian RAS proteins immumoprecipitates RAS protein in yeast cells [Powers et al., Cell, 47:413 (1986)]. Thus, the yeast RAS proteins have the same overall structure and interrelationship as is found in the family of mammalian RAS proteins.

RAS genes have been detected in a wide variety of eukaryotic species, including Schizosaccharomyces pombe, Dictyostelium discoidiem and Drosophila melanogaster [Fukui et al., EMBO, 4:687 (1985); Reymond et al., Cell, 39:141 (1984); Shilo et al., Proc. Natl. Acad. Sci. (USA), 78:6789 (1981); Neuman-Silberberg, Cell, 37:1027 (1984)]. The widespread distribution of RAS genes in evolution indicates that studies of RAS in simple eukaryotic organisms may elucidate the normal cellular functions of RAS in mammals.

Extensive genetic analyses of the RAS1 and RAS2 of S. cerevisiae have been performed. By constructing in vitro RAS genes disrupted by selectable biochemical markers and introducing these by gene replacement into the RAS chromosomal loci, it has been determined that neither RAS1 nor RAS2 is, by itself, an essential gene. However, doubly RAS deficient ($ras1^-$

ras2⁻) spores of doubly heterozygous diploids are incapable of resuming vegetative growth. At least some RAS function is therefore required for viability of S. cerevisiae [Kataoka et al., Cell, 37:437 (1984)]. It has also been determined that RAS1 is located on chromosome XV, 7 cM from ADE2 and 63 cM from HIS3; and that RAS2 is located on chromosome XIV, 2 cM from MET4 [Kataoka et al., Cell, 37:437 (1984)].

Mammalian RAS expressed in yeast can function to correct the phenotypic defects that otherwise would result from the loss of both RAS1 and RAS2 [Kataoka et al., Cell, 40:19 (1985)]. Conversely, yeast RAS are capable of functioning in vertebrate cells [De Feo-Jones et al., Science, 228:179 (1985)]. Thus, there has been sufficient conservation of structure between yeast and human RAS proteins to allow each to function in heterologous host cells.

The missense mutant, $RAS2^{val19}$, which encodes valine in place of glycine at the nineteenth amino acid position, has the same sort of mutation that is found in some oncogenic mutants of mammalian RAS genes [Tabin et al., Nature, 300:143 (1982); Reddy et al., Nature, 300:149 (1982); Taparowsky et al., Nature, 300:762 (1982)]. Diploid yeast cells that contain this mutation are incapable of sporulating efficiently, even when they contain wild-type RAS alleles [Kataoka et al., Cell, 37:437 (1984)]. When an activated form of the RAS2 gene (e.g., $RAS2^{val19}$) is present in haploid cells, yeast cells fail to synthesize glycogen, are unable to arrest in G1, die rapidly upon nutrient starvation, and are acutely sensitive to heat shock [Toda et al., Cell, 40:27 (1985); Sass et al., Proc. Natl. Acad. Sci., 83:9303 (1986)].

S. cerevisiae strains containing $RAS2^{val19}$ have growth and biochemical properties strikingly similar to yeast carrying the IAC or bcyl mutations,

which activate the cAMP pathway in yeast [Uno et al., J. Biol. Chem., 257:14110 (1981)]. Yeast strains carrying the IAC mutation have elevated levels of adenylylate cyclase activity. bcyl⁻ cells lack the regulatory component of the cAMP dependent protein kinase [Uno et al., J. Biol. Chem., 257:14110 (1982); Toda et al., Mol. Cell. Biol., 7:1371 (1987)]. Yeast strains deficient in RAS function exhibit properties similar to adenylylate cyclase-deficient yeast [Toda et al., Cell, 40:27 (1985)]. The bcyl⁻ mutation suppresses lethality in rasl⁻ ras2⁻ yeast. These results suggest that in the yeast S. cerevisiae, RAS proteins function in the cAMP signalling pathway.

Adenylyl cyclase has been shown to be controlled by RAS proteins [Toda et al., Cell, 40:27 (1985)]. RAS proteins, either from yeast or humans, can stimulate adenylyl cyclase up to fifty fold in in vitro biochemical assays. RAS proteins will stimulate adenylyl cyclase only when bound with GTP [Field et al., Mol. Cell. Biol., 8:2159 (1988)].

The phenotypes resulting from the activation of RAS, including sensitivity to heat shock and starvation, are primarily the result of overexpression or uncontrolled activation of the cAMP effector pathway via adenylyl cyclase [Kataoka et al., Cell, 37:437 (1984); Kataoka et al., Cell, 43:493 (1985); Toda et al., Cell, 40:27 (1985); Field et al., Mol. Cell. Biol., 8:2159 (1988)].

Two S. cerevisiae yeast genes, PDE1 and PDE2, which encode the low and high affinity cAMP phosphodiesterases, respectively, have been isolated [Sass et al., Proc. Natl. Acad. Sci., 83:9303 (1986); Nikawa et al., Mol. Cell. Biol., 7:3629 (1987)]. These genes were cloned from yeast genomic libraries by their ability to suppress the heat shock sensitivity in yeast cells harboring an activated $RAS2^{val19}$ gene. Cells lacking

the PDE genes (i.e., pdel⁻ pde2⁻ yeast) are heat shock sensitive, are deficient in glycogen accumulation, fail to grow on an acetate carbon source, and in general have defects due to activation of the cAMP signaling pathway [Nikawa et al., Mol. Cell. Biol., 7:3629 (1987)].

Genetic analysis clearly indicates that RAS proteins have other functions in S. cerevisiae in addition to stimulating adenylyl cyclase [Toda et al., Japan Sci Soc. Press., Tokyo/VNU Sci. Press, pp. 253 (1987); Wigler et al., Cold Spring Harbor Symposium, LIII:649 (1988); Michaeli et al., EMBO, 8:3039 (1989)]. The precise biochemical nature of these functions is unknown. Experiments with other systems, such as S. pombe and Xenopus laevis oocytes, indicate that RAS stimulation of adenylyl cyclase is not widespread in evolution [Birchmeier et al., Cell, 43:615 (1985)]. It is unlikely that RAS stimulates adenylyl cyclase in mammals (Beckner et al., Nature, 317:1 (1985)).

Phosphodiesterases (PDEs) are the enzymes responsible for the degradation of cyclic AMP (cAMP) to AMP and cGMP to GMP. Cyclic AMP is a "second messenger" that mediates the response of cells to a variety of hormones and neurotransmitters including calcitonin, chorionic gonadotropin, corticotropin, epinephrine, follicle-stimulating hormone, glucagon, leutenizing hormone, lipotropin, melanocyte-stimulating hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin.

Cellular concentrations of cyclic adenosine monophosphate (cAMP) are controlled not only by the rate of cAMP production by adenylyl cyclase, but also by the rate of cAMP degradation by phosphodiesterases. In humans, a number of important physiological responses are controlled by cAMP levels, including mental function, smooth muscle relaxation, strength of cardiac

contractility, release of histamine and other immunoreactive molecules, lymphocyte proliferation, and platelet aggregation [Robison et al., Cyclic AMP, Academic Press, New York and London (1971)]. Thus, the range of diseases which can potentially be affected by agents or pharmaceutical compounds which alter cAMP levels include inflammatory processes (e.g., arthritis and asthma), heart failure, smooth muscle cramps, high blood pressure, blood clotting, thrombosis, and mental disorders.

Given the importance of cAMP in the regulation of a variety of metabolic processes, considerable effort has been directed toward developing and evaluating cAMP analogues, as well as inhibitors of phosphodiesterases. One way to modulate cAMP levels in cells is through the modulation of cAMP phosphodiesterase activity. Certain drugs useful in treating heart failure, asthma, depression, and thrombosis, appear to work by inhibiting cAMP phosphodiesterases. The pharmaceutical industry has not been notably successful in finding suitably specific drugs, in part because effective drug screens have not been available. Most tissues contain so many different isoforms of phosphodiesterases that drug screening based on traditional methods involving inhibition of crude tissue extracts is unlikely to yield anything other than a broadly acting inhibitor of phosphodiesterases. Broadly acting inhibitors of cAMP phosphodiesterases, such as theophylline, have many deleterious side effects.

As noted above, PDE inhibitor research has as its goal the development of highly specific PDE inhibitors. This lack of PDE inhibitor specificity is in part attributable to the existence of several distinct molecular forms of PDE present within a single tissue type, indeed, present among the various cell-types comprising a particular tissue type. These

various forms can be distinguished according to substrate specificity (cAMP vs. cGMP), intracellular location (soluble vs. membrane bound), response to calmodulin, and can, in certain instances, be selectively inhibited by various therapeutic agents. Developing agents that will selectively act upon PDEs is directed toward reproducing the desirable effects of cyclic nucleotides, e.g., bronchodilation, increased myocardial contractility, anti-inflammation, yet without causing the undesirable effects, e.g., increased heart rate or enhanced lipolysis.

One approach to screening agents for their potential utility as PDE inhibitors, e.g. drug screening, requires "kinetically pure" preparations of PDE enzymes. That is, the use of whole tissue homogenates or extracts is unlikely to identify inhibitors selective for an individual PDE isozyme because most tissues are heterogeneous with respect to cell type and even many cell types contain multiple PDE isozymes.

At least five different families of PDEs have been described based on characteristics such as substrate specificity, kinetic properties, cellular regulatory control, size, and in some instances, modulation by selective inhibitors. [Beavo, Adv. in Second Mess. and Prot. Phosph. Res. 22:1-38 (1988)]. The five families include:

I	Ca^{2+}/calmodulin-stimulated
II	cGMP-stimulated
III	cGMP-inhibited
IV	cAMP-specific
V	cGMP-specific

Within each family there are multiple forms of closely related PDEs. See Beavo, "Multiple Phosphodiesterase Isozymes Background, Nomenclature and Implications", pp. 3-15 In: Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action, Beavo, J. and Houslay, M.D., Eds.; John Wiley & Sons, New York (1990). See, also, Beavo, TIPS, 11:150 (1990).

Of the many distinct PDE enzymes now recognized, for only certain of the cGMP specific PDEs is complete cDNA sequence information available. With the acquisition of complete structural information for all PDEs, it may be possible to identify and localize (cellular and subcellular distribution) each PDE isozyme and thereby design isozyme-selective PDE inhibitors as therapeutic agents for specific diseases allowing avoidance of untoward side-effects. However, the heterogeneity, instability, and relatively low abundance of some of the PDE isozymes have presented major obstacles in purifying and characterizing these enzymes.

Several methods are presently available for cloning mammalian genes. A standard approach to cloning mammalian genes requires obtaining purified protein, determining a partial amino acid sequence of the purified protein, using the partial amino acid sequence to produce degenerate oligonucleotide probes, and screening cDNA libraries with these probes to obtain cDNA encoding the protein. This method is time consuming and, because of the degeneracy of the probes used, may identify sequences other than those encoding the protein(s) of interest. Many mammalian genes have been cloned this way including, for example, the gene encoding the cGMP phosphodiesterase expressed in retina [Ovchinnikov et al., FEBS, 223:169 (1987)].

A second approach to cloning genes encoding a protein of interest is to use a known gene as a probe to find homologs. This approach is particularly useful when members of a gene family or families are sufficiently homologous. The Drosophila melanogaster dunce phosphodiesterase gene was used, for example to clone rat homologs. Davis et al., Proc. Natl. Acad. Sci. (USA), 86:3604 (1989); and Swinnen et al., Proc. Natl. Acad. Sci. (USA), 86:5325 (1989). Although additional members of one family of phosphodiesterase genes might be cloned once a first member of that family has been cloned, it is never known in advance whether the nucleotide sequences of genes belonging to different phosphodiesterase gene families will exhibit sufficient homology to use probes derived from one family to identify members of another family.

Yet another approach to cloning genes is known as complementation. A number of researchers have reported the isolation of yeast genes by their ability to complement a mutation/defect in the corresponding gene in another yeast. See, for example: McKnight et al., EMBO J., 4:2093 (1985) - Aspergillus nidulans gene encoding alcohol dehydrogenase isolated by its ability to complement an adhl mutation in S. cerevisiae; Sass et al., PNAS (USA), 83:9303 (1986) - S. cerevisiae PDE2 gene isolated by its ability to complement a $RAS2^{val19}$ allele in S. cerevisiae strain TK161-R2V; Nikawa et al., Mol. Cell. Biol., 7:3629 (1987) - S. cerevisiae PDE1 gene isolated by transforming S. cerevisiae strain TK161-R2V; and Wilson, Molec. Cell. Biol., 8:505 (1988) - S. cerevisiae SRA5 gene isolated by virtue of its ability to rescue a RAS^+ sra5-5 S. cerevisiae strain RW60-12C.

Yeast have also been used to isolate non-yeast genes. For example, Henikoff et al., Nature, 289:33 (1981), reported the isolation of a D. melanogaster gene

by complementation of yeast mutants and Lee et al., Nature, 327:31 (1987), reported the isolation of human gene by its ability to complement a mutation in the cdc2 gene in S. pombe. The expression vector employed included a viral (SV40) promoter.

More recently, complementation screening has been used by the applicants herein to detect and isolate mammalian cDNA clones encoding certain types of phosphodiesterases (PDEs). Colicelli et al., PNAS (USA), 86:3599 (1989) reports the construction of a rat brain cDNA library in a Saccharomyces cerevisiae expression vector and the isolation therefrom of genes having the capacity to function in yeast to suppress the phenotypic effects of $RAS2^{val19}$, a mutant form of the RAS2 gene analogous to an oncogenic mutant of the human HRAS gene. A rat species cDNA so cloned and designated DPD (dunce-like phosphodiesterase) has the capacity to complement the loss of growth control associated with an activated $RAS2^{val19}$ gene harbored in yeast strains TK161-R2V. The gene encodes a high-affinity cAMP specific phosphodiesterase that is highly homologous to the cAMP phosphodiesterase encoded by the dunce locus of D. melanogaster.

Relatively few PDE genes have been cloned to date. Of those cloned, most belong to the cAMP-specific family of phosphodiesterases (cAMP-PDEs). See Davis, "Molecular Genetics of the Cyclic Nucleotide Phosphodiesterases", pp. 227-241 in Cyclic Nucleotide Phosphodiesterases: Structure, Regulation, and Drug Action, Beavo, J. and Houslay, M.D., Eds.; John Wiley & Sons, New York; 1990. See also, e.g., Faure et al., PNAS (USA), 85:8076 (1988) - D. discoideum; Sass et al., supra - S. cerevisiae, PDE class IV, designated PDE2; Nikawa et al., supra - S. cerevisiae, designated PDE1; Wilson et al., supra - S. cerevisiae, designated SRA5; Chen et al., PNAS (USA), 83:9313 (1986) - D.

melanogaster, designated dnc^+; Ovchinnikov, et al., supra - bovine retina, designated GMP PDE; Davis et al., supra - rat liver, designated rat dnc-1; Colicelli, et al., supra - rat brain, designated DPD; Swinnen, et al., PNAS (USA), 86:5325 (1989) - rat testis, rat PDE1, PDE2, PDE3 and PDE4; and Livi, et al., Mol. Cell. Biol., 10:2678 (1990) - human monocyte, designated hPDE1. See also, LeTrong et al., Biochemistry, 29:10280 (1990) reporting cloning of a DNA encoding a fragment of a bovine adrenal cGMP stimulated PDE and Thompson et al., FASEBJ., 5(6):A1592 (Abstract No. 7092, 1991) reporting the cloning of a "Type II PDE" from rat pheochromocytoma cells.

Thus, there continues to exist a need in the art for improved cloning procedures effective for isolating genes, both of known and unknown function, for expression products sufficiently kinetically pure so as to be suitable for use in drug improved immunological specificity, and for drug screening methods that do not require kinetically pure protein preparations.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to methods for cloning mammalian genes encoding proteins which can function in microorganisms, particularly yeast, and can modify, complement, or suppress a genetic defect associated with an identifiable phenotypic alteration or characteristic in the microorganism. Provided by the invention are mammalian genes cloned according to the method, as well as products encoded by such genes, and antibodies immunologically reactive with the encoded proteins.

More specifically, the present invention relates to a method of detecting mammalian genes that encode products that modify, complement or suppress a genetic defect in a biochemical pathway in which cAMP

participates, or in a biochemical pathway which is controlled, directly or indirectly, by a RAS protein; to the genes so cloned; to products (nucleic acids, proteins) encoded by the mammalian genes cloned including novel mammalian genes that encode, for example, cAMP phosphodiesterases, proteins that interact with RAS proteins, and other proteins affecting cell growth and maintenance.

The present method can be used to detect a mammalian gene of interest that functions in a microorganism that is genetically altered or defective in a defined manner (an altered microorganism) to correct the genetic alteration or defect and, as a result, modifies an identifiable phenotypic alteration or characteristic associated with the genetic alteration or defect (produces a phenotype more like that of normal or unaltered microorganism). Altered microorganisms illustrating those useful in practice of methods of the invention include *S. cerevisiae* strains TK161-R2V, 10DAB and SKN37 and *S. pombe* strain SP65.

The present invention thus provides novel methods for detecting, in a genetically altered microorganism (such as a mutant yeast or mammalian host cell), a mammalian gene that is capable of modifying a phenotypic alteration associated with a genetic alteration. The steps of the novel methods include: (a) providing mammalian cDNA in an expression vector capable of expressing the mammalian cDNA in the genetically altered microorganism (preferred vectors including an endogenous host cell promoter DNA sequence operatively associated with the cDNA); (b) introducing the expression vector into the genetically altered microorganism; (c) maintaining the genetically altered microorganisms containing the expression vector under conditions appropriate for growth; and (d) identifying genetically altered microorganisms in which the

phenotypic alteration associated with the genetic alteration in the microorganism is modified. Optionally included is the step of isolating the cDNA inserted in microorganisms identified in step (d).

Although use of the present method to clone mammalian genes is described in detail in respect to cAMP phosphodiesterases and proteins that interact with RAS proteins, it can be used to clone and identify other mammalian genes that function in an appropriately-selected altered microorganism to correct, complement or supplement the genetic alteration and, as a result, correct the associated phenotypic alteration. Phenotypic alterations of yeast cells which illustrate the invention include heat shock sensitivity, nitrogen starvation, failure to synthesize normal amounts of glycogen, failure to grow on acetate and failure to sporulate.

In presently preferred forms, the novel DNA sequences comprise cDNA sequences; however, alternate DNA forms such as genomic DNA, and DNA prepared by partial or total chemical synthesis from nucleotides, as well as DNA with deletions or mutations, is also within the contemplation of the invention.

Association of DNA sequences provided by the invention with homologous or heterologous species expression control DNA sequences, such as promoters, operators, regulators and the like, allows for *in vivo* and *in vitro* transcription to form messenger RNA which, in turn, is susceptible to translation to provide the invention proteins, and related poly- and oligo-peptides in large quantities. Presently preferred vectors for use in practice of the invention include plasmids pADNS, pADANS, pAAUN and pAAUN-ATG.

Specifically provided by the invention are mammalian DNA sequences encoding cyclic nucleotide phosphodiesterases and fragments thereof as well as RAS

protein-related DNA sequences which are present as mammalian DNA inserts in bacterial plasmids which are the subject of deposits made April 15, 1991 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 in accordance with U.S. Patent and Trademark Office and Budapest Treaty requirements. Mammalian PDE DNAs made subject of the deposits include:

1. Plasmid pRATDPD in E. coli (A.T.C.C. accession No. 68586) containing a rat brain cDNA insert encoding a dunce-like PDE;

2. Plasmid pJC44x in E. coli (A.T.C.C. accession No. 68603) containing a human glioblastoma cell cDNA insert encoding a cAMP specific PDE;

3. Plasmid pTM3 in E. coli (A.T.C.C. accession No. 68600) containing a human glioblastoma cell cDNA insert encoding a cAMP specific PDE;

4. Plasmid pTM72 in E. coli (A.T.C.C. accession No. 68602) containing a human glioblastoma cell cDNA insert encoding a cAMP specific PDE;

5. Plasmid pPDE21 In E. coli (A.T.C.C. accession No. 68595) containing a human temporal cortical cell cDNA insert encoding a cAMP specific PDE;

6. Plasmid pGB18ARR In E. coli (A.T.C.C. accession No. 68596) containing a human temporal cortical cell cDNA insert encoding a cAMP specific PDE;

7. Plasmid pGB25 In E. coli (A.T.C.C. accession No. 68594) containing a human temporal cortical cell cDNA insert encoding a cAMP specific PDE; and,

8. Plasmid pTM22 In E. coli (A.T.C.C. accession No. 68601) containing a human glioblastoma cell cDNA insert encoding a PDE of unclassifiable family designation.

Mammalian RAS-related DNAs made the subject of deposit include:

9. Plasmid pJC99 in E. coli (A.T.C.C. accession No. 68599) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide;

10. Plasmid pJC265 in E. coli (A.T.C.C. accession No. 68598) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide;

11. Plasmid pJC310 in E. coli (A.T.C.C. accession No. 68597) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide;

12. Plasmid pML5 in E. coli (A.T.C.C. accession No. 68593) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide;

13. Plasmid pATG16 in E. coli (A.T.C.C. accession No. 68592) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide; and,

14. Plasmid pATG29 in E. coli (A.T.C.C. accession No. 68591) containing a human glioblastoma cell cDNA insert encoding a RAS-related polypeptide.

Yeast expression plasmids deposited in connection with the present invention include:

15. Plasmid pAAUN in E. coli (A.T.C.C. accession No. 68590);

16. Plasmid pAAUN-ATG in E. coli (A.T.C.C. accession No. 68589);

17. Plasmid pADANS in E. coli (A.T.C.C. accession No. 68587); and,

18. Plasmid pADNS in E. coli (A.T.C.C. accession No. 68588).

Yeast host cells made the subject of deposit in connection with the present invention include:

19. S. pombe SP565 (A.T.C.C. accession No. 74047);

20. *S. cerevisiae* SKN37 (A.T.C.C. accession No. 74048);

21. *S. cerevisiae* 10DAB (A.T.C.C. accession No. 74049); and,

22. *S. cerevisiae* TK161-R2V (A.T.C.C. accession No. 74050).

Novel protein products of the invention include polypeptides having the primary structural conformation (i.e., amino acid sequence) of phosphodiesterase proteins as well as those having the primary structural conformation of non-phosphodiesterase proteins, including peptide fragments thereof and synthetic peptides assembled to be duplicative of amino acid sequences thereof. Proteins, protein fragments, and synthetic peptides of the invention are projected to have numerous uses including therapeutic, diagnostic and prognostic uses and will provide the basis for preparation of monoclonal and polyclonal antibodies specifically immunoreactive with these proteins. Preferred protein fragments and synthetic peptides include those duplicating regions of the proteins which are not involved in substrate binding functions and the most preferred are those which share at least one antigenic epitope with the proteins of the invention.

Use of mammalian host cells for expression of DNAs of the invention is expected to provide for such post-translational modifications (e.g., truncation, lipidation, glycosylation, and tyrosine, serine or threonine phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention.

Also provided by the present invention are antibody substances (including polyclonal and monoclonal antibodies, chimeric antibodies and single chain antibodies) characterized by their ability to bind with high immunospecificity to the proteins and to their

fragments and peptides, recognizing unique epitopes which are not common to other proteins, especially phosphodiesterases.

Also provided by the present invention are novel procedures for the detection and/or quantification of normal, abnormal, or mutated forms of the proteins as well as nucleic acids (e.g., DNA and mRNA) associated therewith. Illustratively, antibodies of the invention may be employed in known immunological procedures for quantitative detection of the proteins in fluid and tissue samples, of DNA sequences of the invention that may be suitably labelled and employed for quantitative detection of mRNA encoding these proteins.

Among the multiple aspects of the present invention, therefore, is the provision of (a) novel nucleic acid sequences encoding cyclic nucleic acid phosphodiesterase polypeptides and RAS proteins as hereinafter described, and (b) DNA sequences which hybridize thereto under hybridization conditions of the stringency equal to or greater than the conditions described herein and employed in the initial isolation of certain cDNAs of the invention, as well as (c) DNA sequences encoding the same, or allelic variant, or analog polypeptides through use of, at least in part, degenerate codons. Correspondingly provided are viral vectors or circular plasmid DNA vectors incorporating such DNA sequences and procaryotic and eucaryotic host cells transformed or transfected with such DNA sequences and vectors as well as novel methods for the recombinant production of proteins encoded by the DNA sequences through cultured growth of such hosts and isolation of these proteins from the hosts or their culture media.

The present invention further relates to a method of identifying agents that modify or alter (i.e., reduce or stimulate) the activity of the protein products of such mammalian genes expressed in

microorganisms, such as yeast. Identification of such agents can be carried out using two types of screening procedures: one based on biochemical assays of mammalian proteins of known enzymatic function and one based on phenotypic assays for proteins of determined or as yet undetermined function. In the former case, if the encoded proteins are phosphodiesterases, for example, pharmacological screens include assays for chemical agents that alter (i.e., reduce or stimulate) phosphodiesterase activity. In the latter case, if the encoded proteins interact with RAS proteins, for example, pharmacological screens include the assay for agents that reduce or stimulate interactions with RAS proteins. These screening methods can be used with either whole cell preparations or cell extracts and do not require enzyme purification.

Other aspects and advantages of the present invention will be apparent upon consideration of the following detailed description thereof which includes numerous illustrative examples of the practice of the invention, reference being made to the drawing wherein:

FIGURE 1 [Fig. 1(A), 1(B), 1(C) and 1(D)] is a comparative alignment of the nucleotide sequences of the human cDNA inserts of plasmids pJC44X, pTM3, pGB14 and pGB18ARR, wherein lower case letters designate lack of homology and gaps indicate absence of corresponding base positions;

FIGURE 2 [Fig. 2(A), 2(B), 2(C) and 2(D)] is a comparative alignment of the nucleotide sequences of the human cDNA inserts of plasmids pPDE2RR, pTM72, pPDE7 and pPDE 10x-INV, with lower case letters designating lack of homology and gaps indicating the absence of corresponding base positions;

FIGURE 3 is a comparative alignment of the nucleotide sequences of the human cDNA inserts of plasmids pPDE18 and pGB25, with lower case letters designating lack of homology and gaps indicating the absence of corresponding base positions; and

FIGURE 4 [Fig. 4(A) and 4(B)] is a comparative alignment of deduced amino acid sequences of plasmids pTM72 (TM72), pRATDPD, pJC44X, pPDE18 and pPDE21, wherein lower case letters designate non-homologous residues and gaps indicate lack of any residue at the aligned position.

DETAILED DESCRIPTION

The following examples illustrate practice of the invention. Example 1 relates to cloning and identification of mammalian genes by complementation in yeast. Example 2 relates to cloning and identification of mammalian genes by hybridization with mammalian genes cloned by complementation. Example 3 relates to characterization of cloned genes by complementation capacity. Example 4 relates to further characterization of cloned genes by nucleotide sequence analysis. Example 5 relates to screening and identification of agents which alter phosphodiesterase enzymatic activity.

EXAMPLE 1

Cloning of Mammalian Genes By Complementation in Yeast

In its most general form, the methods of the present invention are as follows.

Make mammalian cDNA library

↓

Insert cDNA library into appropriate expression vector

↓

Introduce cDNA-containing expression vector into microorganism (host cells) having genetic alteration associated with identifiable phenotype alteration

↓

Maintain host cells under conditions appropriate for cell growth

↓

Select host cells in which phenotypic alteration is corrected

↓

Recover mammalian gene expressed in selected host cells

↓

Analyze recovered mammalian gene and/or encoded products

First, a cDNA library of mammalian mRNAs is produced using known techniques. This library can be made by cloning double stranded cDNA into an expression vector. The cDNA can be prepared from a pre-existing cDNA library, or it can be prepared by the reverse

transcription of mRNA purified from a tissue or cell line of choice, using standard procedures. Watson et al., In: DNA Cloning, a Practical Approach, IRL Press Oxford (1984)).

The cDNA so obtained is cloned into an expression vector capable of expressing mammalian cDNA inserts as mRNA which in turn can be translated into protein in a host cell of choice, e.g., altered yeast such as S. pombe SP565 (ras1::Leu2/ras1::Leu2) (A.T.C.C. 74047), S. cerevisiae SKN37 (cap::H1S3) (A.T.C.C. 74048), S. cerevisiae 10DAB (pde1$^-$, pde2$^-$) (A.T.C.C. 74049); and S. cerevisiae TK161-R2V (RAS2^{val19}) (A.T.C.C. 74050). Expression vectors which have been used for this purpose are described in the examples which follow and include pAAUN (A.T.C.C. 68590), pAAUN-ATG (A.T.C.C. 68589), pADNS (A.T.C.C. 68587), and pADANS (A.T.C.C. 68588).

Preferred expression vectors contain a transcriptional promoter specific for the host cell into which the vector is introduced, e.g., promoters specific for expression in S. cerevisiae. The transcribed mRNA may utilize the ATG of the cDNA insert as the "start" codon or may express the cDNA product as a fusion protein.

The cDNA library (present as cDNA inserts in a selected expression vector) is introduced into a suitable host cell. This host cell contains genetic alterations which cause the host cell to have an identifiable phenotypic alteration or abnormality associated with the genetic alteration. The host cell may be a eukaryotic microorganism, such as the yeast S. cerevisiae or a mammalian cell.

Known methods, such as lithium acetate-induced transformation, are used to introduce the cDNA-containing expression vector. In the examples that follow, transformation of yeast cells was performed with

lithium acetate. Yeast cells were grown in either rich medium (YPD) or synthetic medium with appropriate auxotrophic supplements (SC). Mortimer et al., In: The Yeast, 1:385 (1969). Ito et al., J. Bacteriol., 153:163 (1983).

The genetic alterations of the selected host cell, may for example, lead to defects in the metabolic pathways controlled by the RAS proteins and the associated readily discernible phenotype may be sensitivity to heat shock or nitrogen starvation, failure to synthesize normal amounts of glycogen, failure to grow on certain carbon sources, failure to sporulate, failure to mate, or other properties associated with defects in the pathways controlled by or controlling RAS proteins. For example, the genetic alteration can be the presence of the $RAS2^{val19}$ gene. Yeast containing such an alteration exhibit heat shock sensitivity, which can be overcome by expression of mammalian genes. In the examples that follow, heat shock experiments were performed by replica plating onto preheated SC plates which were maintained at 55°C for 10 minutes, allowed to cool, and incubated at 30°C for 24-48 hrs.

Other host cells with genetic alterations can be chosen, such as disruptions of the PDE1 and PDE2 genes in S. cerevisiae or disruptions of, or the presence of an activated allele of ras1 in S. pombe. Other genetic alterations in a host cell may be correctable by different subsets of mammalian cDNA genes.

After introduction of the cDNA insert-containing expression vector, host cells are maintained under conditions appropriate for host cell growth. Those host cells which have been corrected for their phenotypic alteration are selected or otherwise identified and the mammalian gene which they express can

be recovered e.g., by transformation of *E. coli* with DNA isolated from the host cell. Segregation analysis in the examples that follow was performed by growing yeast transformants in YPD for 2-3 days, plating onto YPD plates, and replica plating onto YPD, SC-leucine (plasmid selection), and YPD heat shock plates. *E. coli* strain HB101 was used for plasmid propagation and isolation, and strain SCS1 (Stratagene) was used for transformation and maintenance of the cDNA library. Mandel *et al.*, *Mol. Biol.*, 53:159 (1970); Hanahan *J. Mol. Biol.*, 166:557 (1983).

If desired, the mammalian gene can be isolated and sequenced; alternatively, the protein encoded by the gene can be identified and expressed in cultured cells for use in further processes.

Parts A, B, and C below describe the isolation of mammalian genes by complementation in yeast and their subsequent biochemical characterization.

A. Isolation and Biochemical Characterization of a Rat Brain cDNA Encoding a Phosphodiesterase

A rat brain cDNA library was produced and cloned into the yeast expression vector, pADNS. RNA was purified from Sprague-Dawley rat brains by published procedures. Chirgwin *et al.*, *Biochem.*, 18:5294 (1979); Lizardi, *Methods Enzymol.*, 96:24 (1983); Watson *et al.*, *In: DNA cloning, a practical approach, IRL, Press Oxford* (1984). pADNS consists of a 2.2kbp BglII to HpaI fragment containing the *S. cerevisiae* LEU2 gene from YEp213 [Sherman *et al.*, *Laboratory Manual for Methods in Yeast Genetics*, Sherman, F., Fink, G.R. and Hicks, J.B., eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1986)], a 1.6kbp HpaI to HindIII fragment of the *S. cerevisiae* 2μ plasmid containing the origin of replication, and a 2.1kbp SspI to EcoRI fragment containing the ampicillin resistance gene from the

plasmid pUC18. It also contains a 1.5kbp BamHI to HindIII fragment of the modified S. cerevisiae alcohol dehydrogenase (ADH1) promoter [Bennetzen et al., J. Biol. Chem., 257:3018 (1982); Ammerer, Meth. Enzymol., 101:192 (1983)] and a 0.6kbp HindIII to BamHI fragment containing the ADH1 terminator sequences. The promoter and terminator sequences are separated by a polylinker that contains the restriction endonuclease sites NotI, SacII, and SfiI between the existing HindIII and SacI sites.

Double stranded cDNAs were prepared and ligated to NotI linkers, cleaved with NotI restriction enzyme, and cloned into pADNS at the NotI site situated between the alcohol dehydrogenase promoter and termination sequences of the vector. The use of the rare cutting NotI obviated the need for restriction site methylases commonly used in cDNA cloning. cDNAs were ligated to the NotI linker oligonucleotides:

SEQ ID NO: 1
5' - AAGCGGCCGC, and

SEQ ID NO: 2
5' - GCGGCCGCTT.

Approximately $1.5x10^5$ independent cDNA inserts were contained in the library, with an average insert size of 1.5kbp. DNA prepared from the cDNA expression library was used to transform the $RAS2^{val19}$ yeast strain TK161- R2V. The 50,000 Leu^+ transformants obtained were subsequently tested for heat shock sensitivity. Only one transformant displayed heat shock resistance which was conditional upon retention of the expression plasmid. The plasmid, designated pRATDPD, was isolated from this transformant and the 2.17 kb NotI insert was analyzed by restriction site mapping and nucleotide

sequencing. SEQ ID NO: 3 and SEQ ID NO: 4 provide the nucleotide sequence of the insert and the corresponding deduced amino acid sequence. Sequencing was performed using the dideoxy chain termination method. Sanger et al., Proc. Natl. Acad. Sci. (USA), 74:5463 (1977); Biggin, et al., Proc. Natl. Acad. Sci. (USA), 80:3963 (1983)). Genalign was used to align the DPD and dunce sequences (GENALIGN is a copyrighted software product of IntelliGenetics, Inc.; developed by Dr. Hugo Martinez).

A large open reading frame of 562 codons was found. The first ATG appears at codon 46 and a protein which initiates at this codon would have a predicted molecular weight of approximately 60 kDa. This rat gene is designated RATDPD. A search for similar sequences was performed by computer analysis of sequence data banks, and the Drosophila melanogaster dunce gene was found. The two genes would encode proteins with an 80% amino acid identity, without the introduction of gaps, over a 252 amino acid region located in the center of the rat DPD cDNA. The dunce gene has been shown to encode a high affinity cAMP phosphodiesterase. Chen et al., Proc. Natl. Acad. Sci. (USA), 83:9313 (1986); Davis et al., J. Cell Biol., 90:101 (1981); Walter et al., J. Neurosci., 4:494 (1984)).

To demonstrate that the sequences upstream and downstream of the large sequence identity region were in fact contiguous with that region in the mRNA, rather than artifacts of the method for cDNA cloning, the structure of the cloned cDNA was compared with the structure of DPD cDNAs contained in an independently prepared, first strand cDNA population obtained by reverse transcribing total rat brain poly $(A)^+$ RNA with an oligo dT primer. Oligonucleotide primers complementary to sequences located within the identity region, and to sequences near the 5' or 3' ends of the

coding strand, were made. Using either the cloned pRATDPD DNA or the total first strand cDNA material as template, polymerase chain reactions (PCR) were carried out using four different primer sets and the reaction products were analysed by polyacrylamide gel electrophoresis.

Polymerase chain reactions (PCRs) were carried out in thermocycler (Perkin Elmer, Cetus) using a modification of published procedures. Saiki et al., Science, 239:487 (1988). Reaction mixtures contained template DNA (1ng of cloned DNA, or 1μg of total first strand cDNA), 25 pmoles of oligonucleotide primers, 200μM deoxyribonucleotide triphosphates, 10mM Tris HCl (pH 8.4), 50mM KCl, 3mM $MgCl_2$, and 0.01% (w/v) gelatin. The oligonucleotide primers used were:

SEQ ID NO: 5
A, 5' - CACCCTGCTGACAAACCT^{44};

SEQ ID NO: 6
B, 5' - ATGGAGACGCTGGAGGAA^{153};

SEQ ID NO: 7
C, 5' - ATACGCCACATCAGAATG^{676};

SEQ ID NO: 8
D, 5' - TACCAGAGTATGATTCCC^{1449};

SEQ ID NO: 9
E, 5' - GTGTCGATCAGAGACTTG^{1668}; and

SEQ ID NO: 10
F, 5' - GCACACAGGTTGGCAGAC^{2048}.

The superscript numbers indicate position coordinates in pRATDPD SEQ ID NO: 3. Primers C, E and F are non-coding strand sequences. Thirty cycles (1.5 min at 94°C, 3 min at 55°C, and 7 min at 72°C) were performed and the reaction products were analyzed by polyacrylamide gel electrophoresis.

In each case, a fragment of the predicted length was obtained using either of the template DNAs. The band assignments were confirmed by cleavage with restriction endonucleases having recognition sites within the amplified DNA product. Again, in each case, the primary PCR product obtained using either source of template yielded cleavage products of the predicted sizes. The results indicate that the sequence arrangement in the cloned cDNA faithfully reflects the structure of the rat mRNA.

To analyse the biochemical properties of the pRATDPD gene product, crude cell extracts were prepared from one liter cultures of 10DAB yeast cells which had been transformed with either pADNS or pRATDPD. Yeast strain 10DAB cells are <u>pde</u>1$^-$ and <u>pde</u>2$^-$ and do not have a measureable level of endogenous cyclic nucleotide phosphodiesterase activity. Phosphodiesterase activity assays were performed using cAMP as substrate as follows. Yeast cells were grown at 30°C for 36 hours in one liter cultures of synthetic media (SC-leucine). Cells were harvested and washed with buffer C (20mM MES (pH 6.2), 0.1mM $MgCl_2$, 0.1mM EGTA, 1mM β-mercaptoethanol), were resuspended in 30 ml buffer C with 50 μl 1M PMSF, and were disrupted with a French press. The extracts were centrifuged at 1,600g for 10 min and the supernatants were spun at 18,000g for 90 min (4°C). The supernatant was assayed for phosphodiesterase activity as in Collicelli <u>et al.</u>, <u>supra</u>. All the reactions contained Tris-HCl (pH7.5) (100mM), cell extract (50μg protein/ml), 5'-nucleotidase (Sigma, 20ng/ml) and 10mM

Mg^{2+} (unless otherwise stated) and the indicated cyclic nucleotide concentrations. Assays for the cGMP hydrolysis used 1.5μM cGMP. Inhibition studies employed 5μM cAMP in the presence of varying amounts of cGMP up to 500μM. [^{3}H]cAMP and [^{3}H]cGMP were obtained from NEN (New England Nuclear). Reactions were incubated for 10 min at 30°C and stopped with 5X stop solution (250mM EDTA, 25mM AMP, 100mMcAMP).

Control extracts (10DAB with pADNS) showed no cAMP phosphodiesterase activity. Results with the controls were unchanged when performed at 0°C or in the absence of Mg^{2+} and were comparable to results obtained when no extract was added. These results indicate that there is no detectable background phosphodiesterase activity in the non-transformed control strain 10DAB.

In contrast, considerable cAMP phosphodiesterase activity was seen in the 10AB yeast strain transformed with pRATDPD. The rate of cAMP hydrolysis in the resulting transformants was measured as a function of cAMP concentration. The deduced K_m for cAMP is 3.5μM and the calculated V_{max} is 1.1nmol/min/mg.

The assay conditions were varied to ascertain the cation preferences of the enzyme and to determine the ability of calcium and calmodulin to stimulate its activity. In these assays, Mn^{2+} can be utilized as well as Mg^{2+}, and either cation in 1mM final concentration was sufficient. Calcium/calmodulin was unable to stimulate the measured phosphodiesterase activity in the extract. A parallel assay using beef heart phosphodiesterase (Boeringer Mannheim) yielded a 6.5 fold stimulation with the addition of calcium/calmodulin. Finally, no cGMP phosphodiesterase activity was detected in these assays. Beef heart phosphodiesterase was again used as a positive control. In addition, cGMP present in amounts 100 fold over substrate concentrations was unable to inhibit cAMP phosphodiesterase activity.

Biochemical characterization of the pRATDPD cDNA product expressed in yeast indicates that it is a high affinity cAMP specific phosphodiesterase, as is dunce. Davis et al., J. Cell. Biol., 90:101 (1981); Walter et al., J. Neurosci., 4 (1984). In addition, the phosphodiesterase activity is not stimulated by the presence of calcium/calmodulin. This property is shared with dunce and is distinct from some other phosphodiesterases. Beavo, In Advances in second messenger and phosphoprotein research Greengard et al., eds., Raven Press (1988). The two proteins, pRATDPD and dunce, thus appear to have similar biochemical characteristics. However, it should also be noted that pRATDPD encodes a protein product which shows much less significant homology (35%) to dunce beyond the previously described highly conserved core region. These non-conserved sequences could result in an altered or refined function for this mammalian dunce homolog.

The pRATDPD nucleotide sequence as set forth in SEQ ID NO: 3 encodes a methionine codon at position 46 and the established reading frame remains open through to position 563, resulting in a protein with a predicted molecular weight of 60kDa. The same reading frame, however, is open beyond the 5' end of the coding strand. At present, it is not known if the methionine codon at position 46 is the initiating condon for the DPD protein. The coding sequence is interrupted by three closely spaced terminator codons. However, the established reading frame then remains open for an additional 116 codons, followed by more terminator codons, a polyadenylylation consensus signal and a polyadenine stretch. This 3' open reading frame could be incorporated into another dunce-like phosphodiesterase through alternate splicing.

B. Cloning of Human Glioblastoma Cell cDNAs By Complementation

A cDNA library was constructed in λZAP using NotI linkers. In this example, the cDNA derived from mRNA was purified from the human glioblastoma cell line U118MG. Inserts from the λ vector were transferred into two yeast expression vectors pADNS and pADANS. Plasmid pADANS differs from pADNS in that the mRNA transcribed will direct the synthesis of a fusion protein including an N terminal portion derived from the alcohol dehydrogenase protein and the remainder from the mammalian cDNA insert.

The two mammalian cDNA expression libraries so constructed were screened, as in the previous example, for cDNAs capable of correcting the heat shock sensitivity of the S. cerevisiae host TK161-R2V. Several cDNAs were isolated and analysed by sequencing. Four different cDNAs, contained as inserts in plasmids pJC44x, pJC99, pJC265, and pJC310, were thereby discovered, and their DNA sequences are provided in SEQ ID NOs: 11, 13, 15 and 17, respectively.

The insert of pJC44x was shown by computer analysis to be homologous to the rat pRATDPD gene and biochemical analysis of cellular lysates demonstrated that it encodes a cAMP phosphodiesterase. The inserts in pJC99, pJC265, and pJC310, show no significant homology to previously isolated genes.

C. Cloning of Human Glioblastoma Cell Phosphodiesterase cDNAs By Complementation

The human gliobastoma cDNA expression library previously described was screened for cDNAs capable of correcting the heat shock sensitivity of the phosphodiesterase deficient yeast strain 10DAB. Several cDNAs were so isolated and analyzed by nucleotide and restriction endonuclease sequencing mapping. The cDNA

insert in pTM22 encodes a novel human gene. Its nucleotide sequence and deduced amino acid sequence are shown in SEQ ID NOs: 19 and 20.

From a computer analysis of the nucleotide sequence of the pTM22 insert putatively encodes a protein homologous to various cAMP phosphodiesterases, such as the bovine Ca^{2+}/calmodulin dependent cAMP phosphodiesterase and the rat DPD phosphodiesterase described in Example 1A. Biochemical analysis has proven that the isolated DNA encodes a novel cAMP phosphodiesterase.

Sequences related to the pTM22 insert were found to be expressed in the human heart as well, and splicing variants of TM22 were isolated from a human heart cDNA library using pTM22 insert sequences as a nucleic acid hybridization probe.

Plasmid pTM22 was unable to correct the heat shock sensitivity of $\underline{RAS2}^{val19}$ yeast strains, i.e., of TK161-R2V. It thus appears that the $\underline{pde1}^-$ $\underline{pde2}^-$ yeast strain 10DAB is more sensitive to phenotypic reversion by mammalian cAMP phosphodiesterase clones than is the $\underline{RAS2}^{val19}$ yeast strain.

Several other human glioblastoma cDNAs, isolated as inserts in the plasmids designated pTM3 and pTM72, were similarly characterized. These two different cAMP phosphodiesterase cDNAs were found to be very closely related to, but distinct from, the pRATDPD cDNA insert and the pJC99 cDNA insert. Their nucleotide sequences and deduced amino acid sequences are shown in SEQ ID NOs: 21 and 23, respectively.

Biochemical analysis of cell lysates has established that the cDNAs of pTM3 and pTM72, pJC44x and pRATDPD encode rolipram sensitive cAMP phosphodiesterases.

D. Kinetic Analysis of pPDE cDNA Expression Products

Samples containing approximately 10^{10} transformed S. cerevisiae 10DAB cells expressing the human cDNAs inserted in pJC44x, pTM3, a pTM22-like plasmid (designated L22 Met and including a 1.7 kb fragment insert derived from pTM22 and encoding the PDE activity) and pAD72 (a TM72-like clone) were re-suspended in 2.5 ml PBS and disrupted by vortexing in the presence of glass beads at 4°C. The supernatant fraction following centrifugation for 5 min at 12,000 xg was the source for enzyme in these studies.

Phosphodiesterase activity was determined as described, with minor modifications, in Davis et al., J. Cyc. Nuc. Res., 5:65-74 (1979). Incubation mixtures contained 40 mM Tris pH 8.0, 1 mM EGTA, 5 mM $MgCl_2$, 0.1 mg/ml BSA, diluted yeast extract, [^{3}H]cAMP, and varying amounts of unlabeled cyclic nucleotides to a final volume of 0.25 ml. Reactions were terminated by the addition of 0.25 ml stop buffer containing 0.5 M carbonate pH 9.3, 0.5 M NaCl and 0.1% SDS. Nucleotide products and unreacted substrates were separated on boronate columns (8 X 33 mm). The products were eluted from the boronate columns with sorbitol into scintillation vials for tritium analysis. All kinetic data represent measurements of initial rates, determined by incubations for multiple time intervals at suitable dilutions of enzyme. Analysis of kinetic data by the Lineweaver-Burk transformation of the Michaelis-Menten kinetic model demonstrates a linear double reciprocal plot indicative of a simple kinetic model for each enzyme tested. Cyclic nucleotide concentrations varied from 3×10^{-8} to 1×10^{-4} M [cAMP]. The results obtained are shown in Table 1, below.

TABLE 1

Preliminary Kinetic Analysis of Human Cyclic Nucleotide Phosphodiesterases Derived by Yeast Complementation

Clone Name	K_m [1]	V_{max} [2]
pJC44x	3 µM	830
pAD72	1.3 µM	670
pTM3	4.5 µM	16
pL22Met	0.1 µM	240

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1 expressed as µM cAMP
2 expressed as nmol/min/10^{12} cells

E. Cloning of Human Glioblastoma Cell RAS-related cDNAs By Complementation in Yeast

In this example, four human glioblastoma cell cDNAs were isolated which do not encode PDEs. They were obtained by complementation of two genetically altered *S. cerevisiae* and *S. Pombe* yeast strains.

Clone S46 was selected by complementation in *S. cerevisiae* strain RS60.15B. This strain contains a mutant allele of RAS2, $RAS2^{val19ala15}$, which renders cells unable to grow at 36°C [Powers *et al.*, Mol. Cell Biol., 9:390-395 (1989)], because such cells are defective in RAS function at elevated temperatures. Human cDNAs from a human glioblastoma cell library were selected that could complement this defect. One cDNA found this way was designated S46. Its nucleotide and deduced amino acid sequences are provided in SEQ ID NOs: 25 and 26. The deduced amino acid sequence is homologous to a *Xenopus laevis* gene that encodes a known protein kinase, the S6 protein kinase.

Plasmid pML5 was selected by complementation in another *S. cerevisiae* strain, SKN37. This particular strain contains a disrupted allele of CAP, cap::HIS3. CAP encodes an adenylylyl cyclase associated protein of

undetermined function. [Field et al., Cell, 61:319-327 (1990)]. As a consequence of this gene disruption, SKN37 fails to grow in medium rich in amino acids [Gerst et al., Mol. Cell Biol., 11:1248-1257 (1991)]. Human cDNAs were selected that could complement this defect. One cDNA insert found this way is present in pML5. Its nucleotide and deduced amino acid sequences are provided in SEQ ID NOs: 27 and 28. Its coding capacity is not yet certain.

Plasmids pATG16 and pATG29 were selected by complementation in the S. pombe diploid strain SP565. This strain is homozygous for disruptions of ras1 (ras1::LEU2). As a consequence, this strain fails to sporulate [Fukui et al., Cell, 44:329-336 (1986)] and human cDNAs were selected that could complement this defect. DNA sequence information for the inserts of pATG16 and pATG29 is set forth in SEQ ID NOs: 29 and 31, respectively. These genes have unknown function. The vector used for screening in S. pombe differs from the vector used for screening in S. cerevisiae. This vector, pAAUN-ATG, utilizes an S. pombe specific promoter, the adh promoter, and was constructed as follows. The cloning vector pAAUN was derived from plasmid pART1 (McLeod et al., EMBO J., 6:729-736 (1987) by replacing the S. cerevisiae LEU2 gene with a 1.8 kbp HindIII ura4 fragment from S. pombe and adding NotI linkers at the SmaI site of the polylinker (PL) derived from Viera et al., Methods in Enzymology, 153:3-11 (1987). pAAUN contains the S. pombe adh promoter for gene expression and an ARS region for DNA replication. Plasmid pAAUN-ATG, was derived from plasmid pART8, obtained from David Beach, at Cold Spring Harbor Laboratory, and from pAAUN. The fragment of BamHI-EcoRV in pAAUN was replaced with the fragment of BamHI and EcoRV in pART8 which had a ATG start codon supplied by NdeI site in the polylinker.

EXAMPLE 2

Cloning and Identification of Mammalian Genes By Hybridization With Mammalian Genes Cloned By Complementation

This example relates to the cloning and identification of additional mammalian genes by hybridization to probes having sequences derived from the genes described in Example 1, i.e., those genes cloned via complementation in yeast.

Low and high stringency hybridizations were done under the same conditions for 12 to 16 hours at 65°C in an aqueous solution consisting of 6 times the normal concentration of sodium citrate (SSC), 5 times the normal concentration of Denhardt's solution, 0.5% sodium dodecyl sulfate (SDS), 0.05 mg/ml of denatured salmon sperm DNA and probe. After hybridization, nitrocellulose filters are incubated for five minutes in 2xSSC, 0.5% SDS, at room temperature, and for twenty minutes in fresh 2xSSC, 0.5% SDS, at 60°C.

For high stringency hybridizations only, a third wash is performed for twenty minutes at 60°C in 0.1xSSC, 0.1% SDS. The normal concentration of SSC is 0.15M sodium citrate and 0.15M sodium chloride, and the normal concentration of Denhardt's solution is 0.2 g/l Ficoll, 0.2 g/l polyvinyl/pyrrolidone, and 0.2 g/l bovine serum albumin.

Plasmids pPDE7, pPDE10X inv, and pPDE2RR were isolated by low stringency hybridization screens of a human temporal lobe cDNA library using the pRATDPD insert as probe. Nucleotide sequence (SEQ ID NOs: 33, 34 and 35, respectively) comparisons indicate that the inserts are representatives of the same genetic locus as the insert in pTM72.

Plasmids pGB14 and pGB18ARR were obtained in the same manner. DNA sequence analysis (SEQ ID NOs: 37 and 39, respectively) revealed that they are representatives of the same genetic locus as the inserts in pTM3 and pJC44x.

Plasmid pGB25 was also obtained by low stringency hybridization using the pRATDPD insert as a probe. Judged by its nucleotide sequence as set out in SEQ ID NO: 40 it represents a novel member of PDE family IV.

The cDNA insert of pGB25 was used as a probe to obtain pPDE18 and pPDE21. The cDNA of pPDE18 (SEQ ID NO: 41) represents the same locus as that of pGB25 (SEQ ID NO: 43) and contains more sequence information than the pGB25 cDNA. The pPDE21 insert represents a fourth member of PDE family IV.

No biochemical data on expression products of these clones has yet been obtained. Their assignment to class IV is made solely based on sequence relationships.

EXAMPLE 3

Characterization of Cloned Genes By Complementation Capacity

This example relates to the further characterization of the genes cloned in Example 1 by their capacity to complement yeast strains other than the yeast strain originally used to clone the gene.

For example, 10DAB cells ($pde1^-$ $pde2^-$) were transformed with the DPD expression plasmid, pRATDPD, and assayed for heat shock sensitivity. Expression of the rat DPD gene indeed rendered this host resistant to heat shock. Similarly, pJC44x was able to correct the phenotypic defects of this $pde1^-$ $pde2^-$ yeast strain.

In contrast, pJC99, pJC265, and pJC310 were unable to do so. This suggests that the cDNAs of the latter inserts do not encode cAMP phosphodiesterases. Rather, these genes encode proteins of undetermined function which appear to be able to correct phenotypic defects in yeast with activated RAS proteins as reflected by their capacity to complement yeast strain TK161-R2V.

The procedures described below operate to establish that cDNAs need not be cloned by complementation (or by hybridization to DNAs cloned by complementation) in order to be functional in a genetically altered host. Put another way, the following procedures demonstrate that chemical agent screening methodologies according to the present invention need not involve initial direct or indirect cloning of pertinent DNAs by means of complementation.

A. Yeast Phenotype Complementation by Expression of a cDNA Encoding Bovine Brain CaM-PDE

Plasmid pCAM-40 (in *E. coli*, A.T.C.C. accession No. 68576) includes a bovine brain cDNA insert encoding a 61 kDa Ca^{2+}/calmodulin stimulated cyclic nucleotide phosphodiesterase.

A 2.2 kb cDNA fragment, adapted for insertion into yeast expression plasmids pADNS and pADANS was derived from the plasmid pCAM-40 by polymerase chain reaction. Briefly, the following PCR amplification was employed to alter the pCAM-40 DNA insert to align it appropriately with the ADH1 promoter in the vectors.

One oligonucleotide primer (Oligo A) used in the PCR reaction

SEQ ID NO: 45

5'-TACGAAGCTTTGATGGGGTCTACTGCTAC-3'

anneals to the pCaM-40 cDNA clone at base pair positions 100-116 and includes a HinDIII site before the initial methionine codon. A second oligonucleotide primer (Oligo B)

SEQ ID NO: 46
5'-TACGAAGCTTTGATGGTTGGCTTGGCATATC-3'

was designed to anneal at positions 520-538 and also includes a HinDIII site two bases before a methionine codon. The third oligonucleotide

SEQ ID NO: 47
5'-ATTACCCCTCATAAAG-3'

annealed to a position in the plasmid that was 3' of the insert. For one reaction, Oligo A and Oligo C were used as primers with pCAM-40 as the template. The nucleic acid product of this reaction included the entire open reading frame. A second reaction used Oligo B and Oligo C as primers on the template pCAM-40 and yielded a nucleic acid product that lacked the portion of the cDNA sequence encoding the calmodulin binding domain. These amplified products were digested with HinDIII and NotI and ligated to HinDIII/NotI-digested yeast expression vectors pADNS and pADANS. Plasmid clones containing inserts were selected and transformed into S. cerevisiae strain 10DAB by lithium acetate transformation.

Transformed yeast were streaked in patches on agar plates containing synthetic medium lacking the amino acid leucine (SC-leucine agar) and grown for 3 days at 30°C. Replicas of this agar plate were made with three types of agar plates: one replica on SC-leucine agar, one replica on room temperature YPD agar, and three replicas on YPD agar plates that had been warmed to 56°C. The three warmed plates were maintained

at 56°C for 10, 20, or 30 minutes. These replicas were than allowed to cool to room temperature and then all of the plates were placed at 30°C. Yeast transformed with plasmids constructed to express the CaM-PDE were resistant to the thermal pulse. More specifically, both the construct designed to express the complete open reading frame and that designed to express the truncated protein (including the catalytic region but not the calmodulin binding domain), in either pADNS or pADANS, complemented the heat shock sensitivity phenotype of the 10DAB host cells, i.e., rendered them resistant to the 56°C temperature pulse.

B. Biochemical Assay of Expression Products

The CaM-PDE expression product was also evaluated by preparing cell-free extracts from the yeast and measuring the extracts' biochemical phosphodiesterase activity. For this purpose, 200 ml cultures of transformed yeast were grown in liquid SC-leucine to a density of about 6 million cells per ml. The cells were collected by centrifugation and the cell pellets were frozen. Extracts were prepared by thawing the frozen cells on ice, mixing the cells with 1 ml of PBS and an equal volume of glass beads, vortexing them to disrupt the yeast cells, and centrifuging the disrupted cells at approximately 12,000 x g for 5 min to remove insoluble debris. The supernatant was assayed for phosphodiesterase activity.

Extracts of yeast cells, up to 50 µl, were assayed for phosphodiesterase activity in 50mM Tris (pH 8.0), 1.0 mM EGTA, 0.01 mg/ml BSA (bovine serum albumin), [^{3}H]-cyclic nucleotide (4-10,000 cpm/pmol), and 5 mM $MgCl_2$ in a final volume of 250 µl at 30°C in 10 x 75 mm glass test tubes. The incubations were terminated by adding 250 µl of 0.5 M sodium carbonate

(pH 9.3), 1M NaCl, and 0.1% SDS. The products of the phosphodiesterase reaction were separated from the cyclic nucleotide by chromatography on 8 x 33 mm columns of BioRad Affi-Gel 601 boronic acid gel. The columns were equilibrated with 0.25 M sodium bicarbonate (pH 9.3) and 0.5 M NaCl. The reactions were applied to the columns. The assay tubes were rinsed with 0.25M sodium bicarbonate (pH 9.3) and 0.5 M NaCl and this rinse was applied to the columns. The boronate columns were washed twice with 3.75 ml of 0.25 M sodium bicarbonate (pH 9.3) and 0.5 M NaCl followed by 0.5 ml of 50 mM sodium acetate (pH 4.5). The product was eluted with 2.5 ml of 50 mM sodium acetate (pH 4.5) containing 0.1 M sorbitol and collected in scintillation vials. The eluate was mixed with 4.5 ml Ecolite Scintillation Cocktail and the radioactivity measured by liquid scintillation spectrometry.

Both the construct designed to express the complete open reading frame and that designed to express a truncated protein, in either pADNS or pADANS, expressed active protein as determined by biochemical phosphodiesterase assay of cell extracts using cAMP substrate.

C. Yeast Phenotype Complementation by Expression of a cDNA Encoding a Bovine Adrenal cGS-PDE

The plasmid p3CGS-5 (A.T.C.C. 68579) which contains a 4.2-kb DNA fragment encoding the bovine cGMP stimulated cyclic nucleotide phosphodiesterase (cGS-PDE), was adapted for cloning into pADNS and pADANS by replacing the first 147 bases of the cDNA with a restriction site suitable for use in the insertion into the plasmids. The oligonucleotide BS1, having the sequence

SEQ ID NO: 48

5'-TACGAAGCTTTGATGCGCCGACAGCCTGC-3',

encodes a HinDIII site and anneals to positions 148-165 of the cDNA insert. An oligonucleotide designated BS3

SEQ ID NO: 49

5'-GGTCTCCTGTTGCAGATATTG-3',

anneals to positions 835-855 just 3' of a unique NsiI site. The resulting PCR-generated fragment following digestion with HinDIII and NsiI was then ligated to HinDIII- and NsiI-digested p3CGS-5 thereby replacing the original 5' end of the bovine cDNA. A plasmid derived from this ligation was digested with HinDIII and NotI to release the modified cDNA insert. The insert was cloned into pADNS and pADANS at their HinDIII and NotI sites. These plasmids were then transformed into the yeast strain 10DAB by the lithium acetate method and the transformed cells were grown and subjected to elevated temperatures as in Section A, above. Both transformations resulted in complementation of the heat shock sensitivity phenotype of the 10DAB host cells.

D. Biochemical Assay <u>of Expression Product</u>

The expression of the cGS-PDE was also evaluated by preparing cell-free extracts from the yeast and measuring the extracts' biochemical phosphodiesterase activity. For this purpose, 50 ml cultures of transformed yeast were grown in liquid SC-leucine to a density of about 10 million cells per ml. Sherman <u>et al</u>., <u>Methods in Yeast Genetics</u>, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1986). The cells were collected by centrifugation, the cell pellets were washed once with water, and the final cell pellets

were frozen. To prepare an extract, the frozen cells were thawed on ice, mixed with 1 ml of PBS and an equal volume of glass beads, vortexed to disrupt the yeast cells, and centrifuged to remove debris. The supernatant was then assayed for phosphodiesterase activity as in Section B, above.

Constructs in either pADNS or pADANS expressed active protein as determined by biochemical phosphodiesterase assay of cell extracts using cGMP.

EXAMPLE 4

Further Characterization of Cloned Genes By Nucleotide Sequence Analysis

This example describes the family-relatedness of the various human PDE clones described in the preceeding examples. These clones include both those obtained by complementation and those obtained by hybridization.

COMPLEMENTATION	HYBRIDIZATION
pJC44x	pPDE7
pTM22	pPDE10 X inv
pTM3	pPE2RR
pTM72	pGB14
	pGB18ARR
	pGB25
	pPDE21
	pPDE18

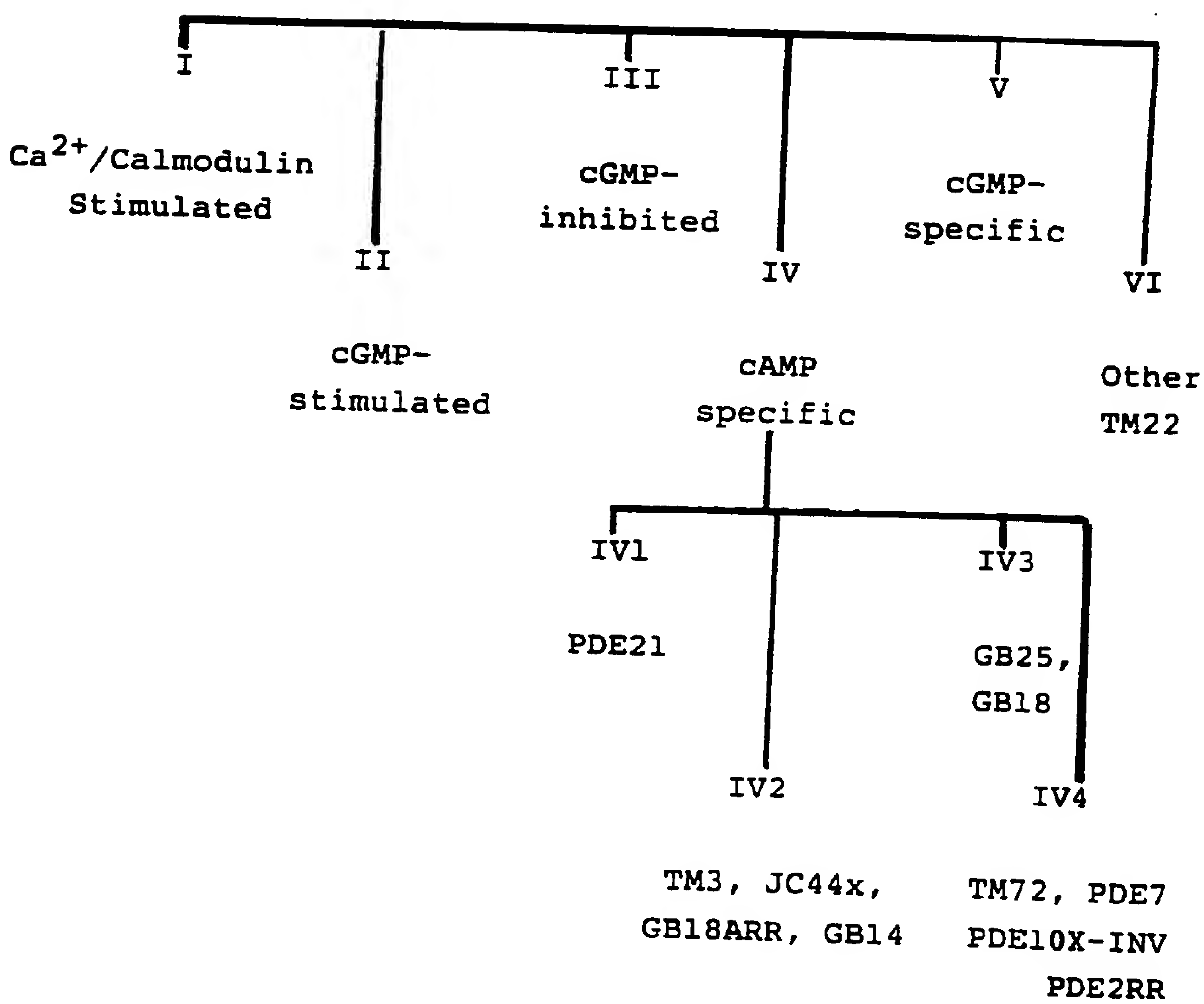
The uniqueness of its DNA sequence indicates that the pPDE21 cDNA derives from a locus herein designated PDE Class IV1. Plasmid pTM3, pJC44x, pGB18ARR and pGB14 cDNA all derive from the same genetic locus, herein designated PDE Class IV2. Evidence for this relation is shown in Figure 1 demonstrating virtual sequence identity.

Likewise pTM72, pPDE7, pPDE10Xinv, and pPDE2RR cDNAs all derive from a genetic locus, herein designated PDE Class IV4. Evidence for this relation is shown in Figure 2 demonstrating virtual sequence identity.

The cDNAs of pGB25 and pPDE18 derive from yet another genetic locus, herein designated PDE class IV3. Evidence of this relation is shown in Figure 3 which demonstrates virtual sequence identity.

This relationship can be visualized as:

Cyclic Nucleotide Phosphodiesterases



The sequences derived from any given locus are not precisely identical. These sequence deviations can derive from a number of different sources including, sequencing errors, true polymorphisms in human populations, cloning artifacts, and differences in splicing patterns. Differences in splicing patterns perhaps account for the major differences in the pTM3 and pJC44x inserts. The pJC44x insert cDNA also may contain some cloning artifacts. Sequence errors, not only for the clones described above, but also for published PDE sequences may have occurred. Naturally occuring sequence variations, or polymorphisms, may also account for the observed results. This introduces some uncertainty into the deduced amino acid sequence of the product of a given locus. Accordingly, it is to be appreciated that the nucleotide sequences claimed encompass not only the specific sequences claimed but also DNA sequences which are substantially the same as those provided herein for cloned cDNAs of interest.

The PDE family IV classes 1-4 comprise a gene family that is related to the rat DPD. The evidence for this is based on the similarity of the encoded amino acid sequences of representatives of this family.

Ostensibly, there are just four members of PDE family IV. In the description that follows, the term "human <u>dunce</u> PDEs" refers to all members of family IV, i.e., the genes that show nucleotide sequence homology to the <u>Drosophila</u> <u>dunce</u> PDE.

Only a subset of the members of a gene family may be expressed in any given tissue. Attempts to quantitate a gene family by studying cDNAs cloned from one, or only a few, tissues may therefore underestimate the total number of members of the family. However, analysis of genomic DNA avoids this problem. Human genomic DNA was used as a substrate in PCR reactions performed in parallel, each containing one of a number

of different pairs of oligonucleotides corresponding to various regions of the family IV PDEs. The regions chosen were those strongly conserved in evolution and/or present in all the known members of this human gene family. The oligonucleotides were comprised of mixtures representing the full degeneracy of codons specifying the desired amino acid sequence. The vast majority of the oligonucleotide pairs tested produced several different PCR products, which were heterogenous in length but always equal to or longer than those produced from the corresponding cDNA. However, two pairs produced only products identical in length to the cDNA. The longer, heterogenous populations of products resulted from the priming of oligonucleotide pairs located on two separate exons. The two oligonucleotide pairs that produced identical length products primed off the same exon.

To confirm that the heterogenous fragment populations truly represented priming from separate exons, human family IV PDE genomic DNA clones were used as substrates in control PCR reactions. In these experiments, each of these clones produced a single PCR product, which was always equal in length to one of the heterogenous products obtained from genomic DNA.

The products from one of the reactions using oligonucleotides pairs that primed from one exon were cloned and sequenced. The oligonucleotides used were

SEQ ID NO: 50

5'TTYAARTCTNYTNCARGRNGA, and

SEQ ID NO: 51

5'ACNATRTCTRATNACCATYTT

wherein: N is any of the four nucleotides; Y is C or T; and R is G or A. This corresponds to the fully degenerate codons specifying four potential amino acid sequences

FKLLQ(E/G)EN

represented by SEQ ID NOs: 52 and 53, and

DMVID(M/I)V

represented by SEQ ID NOs: 54 and 55

respectively, the two conserved domains boxed in Figure 4. Using these primers, four different PCR clones were obtained, each corresponding in nucleotide sequence to one of the members of the known human family IV PDEs. The numbers of clones falling into each category were as follows:

TYPE	TOTALS
TM72 type (Class IV4):	16
JC44 type (Class IV2):	29
PDE18 type (Class IV3):	25
PDE21 type (Class IV1):	9
Total:	79

Assuming that the human genes each exist as single copies (which is consistent with this analysis of the available genomic clones), the four PCR products should be obtained ideally at equal frequency. The slightly skewed distribution obtained here probably reflects differing efficiencies in the production of these products in a PCR reaction due to mismatches with the PCR oligonucleotides. However, all four previously known genes were represented in the final PCR product, and no new sequences were identified. Therefore, the human PDE family IV most likely consists of a total of

four members. Had this method identified a novel member of the family, the PCR clone could have been used as a probe to isolate cDNA clones. It is possible, however, that this family IV family has other members which have diverged at the codons specifying the amino acids sequences boxed in Figure 4.

The cDNA insert pTM22 represents a genetic locus that is not a member of family IV. The evidence for this is that while the deduced amino acid sequence of the pTM22 insert has the general features expected of a cAMP phosphodiesterase, this sequence is not particularly closely related to the sequences of members of the family IV or of the family I, the Ca^{2+}/calmodulin sensitive PDEs, or of the other known PDE families.

EXAMPLE 5

Screening and Identification of Agents Which Alter Enzymatic Activity

In their most general form, the pharmacological screening methods of the invention permit screening for agents that reduce or stimulate the activity of any mammalian protein whose presence or expression in an altered microbial host cell in which a genetic alteration is associated with an identifiable phenotypic alteration results in correction of the phenotypic alteration. Two general types of screens are possible. Both methods are applicable to either living cells, or cell preparations, or cell extracts.

A. Identification of Agents That Affect Proteins of Known Activity

The first type of pharmacological screen is applicable when the mammalian gene encodes a protein of known and assayable biochemical function. The mammalian gene is first expressed in a microbial host by utilizing an appropriate host expression vector of the type

already described. Either whole cells or extracts of host cells can be used. Extracts are prepared, using known techniques, i.e., the cells are disrupted and their cellular constituents released. Crude cellular extract of purified mammalian protein is assayed for the known biochemical function in the presence of agents, the effects of which on the protein are to be assessed. In this manner, agents which inhibit or stimulate the activity of the mammalian protein can be identified.

This type of procedure can be carried out to analyze the effects of selected agents on mammalian cAMP phosphodiesterases. For example, a yeast strain lacking both endogenous PDE1 and PDE2 genes can be used as the host cell, into which cDNA encoding mammalian cAMP phosphodiesterase is introduced in an appropriate expression vector and expressed. Such a host cell is particularly useful because there is no endogenous (background) cAMP phosphodiesterase activity. [Colicelli et al., Proc. Natl. Acad. Sci. (USA), 86:3599 (1989)]. Hence, activity of the mammalian enzyme can be cleanly assayed even in crude cell extracts. This procedure is illustrated below, in which it is demonstrated that the enzymatic activity of the rat DPD gene product is readily inhibited by the pharmacological agents Rolipram and R020 1724, but not as readily by the pharmacological agent theophylline.

The genes and cells described in the preceeding examples can be used to identify chemical compounds which inhibit the activity of a known enzyme, the rat DPD phosphodiesterase. To test the efficiency of known inhibitory compounds, cell free extracts were made. Yeast cells deficient in endogenous phosphodiesterase (10DAB), and expressing the rat DPD or yeast PDE2 genes from the described expression vector, were used. One liter cultures were harvested, washed in

buffer C (20mM MES(pH 6.2)/0.1mM $MgCl_2$/0. 1mM EGTA/1mM 2-mercaptoethanol), resuspended in buffer C containing 1.5 mM phenylmethylsulfonyl fluoride, and disrupted in a French press at 4°C. Cell extracts were clarified at 100g for 10 minutes and at 18000g for 90 minutes. PDE activities were assayed as published (Charbonneau et al., Proc. Natl. Acad. Sci. (USA), 83:9308-9312 (1986); Tempel et al., Proc. Natl. Acad. Sci. (USA), 80:1482-1486 (1983)) in a reaction mix containing 50μg of cell protein/ml, 100mM Tris (pH 7.5), 10mM Mg^{++}, 5μM cAMP, 5'-nucleotidase and [^{3}H] cAMP. AMP was separated from cAMP using AG1-X8 resin from Bio Rad. About 10^4 cpm were obtained for 10 min reactions and backgrounds (phosphodiesterase deficient-yeast or no extract) were about 300 cpm. The cytosolic fraction was assayed in the presence or absence of inhibitory compounds. These assays measure the amount of adenosine 5' monophosphate (AMP) produced by phosphodiesterase-catalysed hydrolysis of adenosine 3', 5'-cyclic adenosine monophosphate (cAMP). For each extract the percent inhibition for various concentrations of known inhibitors is given in Table 2. The percent inhibition represents the decrease in phosphodiesterase activity relative to measurements made in the absence of inhibitors. Rolipram, and the related compound R020 1724, were the most effective inhibitors of DPD activity.

TABLE 2

Inhibition of Phosphodiesterases by Chemicals

Phospho-diesterase	Agent	Concen-tration (μM)	Inhibition (%)
PDE2	Theophylline	250	0.0
	IBMX	250	0.0
	R020 1724	100	3.0
	Rolipram	100	0.0
rat DPD	Theophylline	250	42.
	IBMX	250	87.
	R020 1724	0.1	35.
		1.0	52.
		10.0	79.
		100.0	92.
	Rolipram	0.1	50.
		1.0	72.
		10.0	92.
		100.0	95.

This analysis can, of course, be extended to test new or related chemical compounds for their ability to inhibit PDE activity, or the activity of another phosphodiesterase expressed in this system. Clearly, this form of analysis can also be extended to other genes cloned and expressed in a similar manner for which there is an assayable enzymatic activity.

Phosphodiesterase activity was determined as described in the previous table using 0.04 and 1.0 μM cAMP for pL22 Met and pJC44x, respectively. These concentrations of cAMP were specifically chosen to be below the K_m for their respective enzymes. Thus, the EC_{50} closely approximates the inhibitor constant or K_i of each enzyme. All kinetic data represent initial velocities of enzyme catalysis.

TABLE 3

Inhibitor Sensitivities of Human Cyclic AMP Phosphodiesterases Derived by Yeast Complementation

	EC_{50}[1]	
Agent	pJC44x	pL22 Met
cAMP	3	0.2
cGMP	>300	>300
Rolipram	0.4	>300
RO 20-1724	3	>300
Milrinone	30	30
Theophylline	300	>300

1 EC_{50} = Inhibitor concentration at 50% enzyme velocity, concentration expressed in μM

The following procedure was applied to the screening of whole transformed host cells. The yeast strain 10DAB was transformed with the expression vector pAD72, which expresses a human family IV phosphodiesterase, i.e., a cAMP specific PDE. This transformed strain was grown in SC-leucine medium for three days at 30° C. These cultures achieved a cell density of about 50 million cells per ml. Aliquots of this culture (300 μl) were taken and mixed with 4.8 μl 10% DMSO or 10% DMSO containing an appropriate concentration of phosphodiesterase inhibitor. The treated cultures were then incubated for two hours at 30°C, after which two 3 μl aliquots were removed and transferred to an SC-leucine agar plate. Then, a 100 μl aliquot was removed from the treated cultures and transferred to a glass 12 x 75 mm test tube and the test tubes were incubated at 50°C in a mineral oil-containing hot block for 30 min. The test tubes were removed from the hot block and placed at room temperature. Two 3 μl aliquots were removed and transferred to an SC-leucine plate. The agar plates were then incubated at 30°C and examined at various times to evaluate growth.

Yeast treated with 10% DMSO alone showed a slight decrease in the number of viable cells following the 50°C heat treatment. Treatment of cells with Rolipram reduced the number of viable cells, such that at 100 μM Rolipram, less than 10 out of approximately 150,000 cells remained viable. Milrinone up, to 100μM, had no observable effect on the culture.

B. Identification of Agents Which Affect Proteins of Unspecified Function

This example illustrates the use of the genes and methods described above for use in identifying chemical compounds which affect the function of the encoded mammalian proteins expressed in yeast, even when the function of that protein has not yet been determined.

10DAB cells, which are phosphodiesterase deficient, are sensitive to heat shock. As already discussed, when these cells acquire the capacity to express the cDNA of pRATDPD, they become resistant to heat shock. 10DAB cells expressing the cDNA of pRATDPD were maintained in rich medium (YPD) for three days at stationary phase. These cultures were then treated with Rolipram, a known phosphodiesterase inhibitor, for 40 minutes at a final concentration of 100μM. Control cultures were not treated with any inhibitor. These cultures were then heat shocked in glass tubes at 50°C for 30 minutes. One microliter of each culture was plated. Cultures treated with Rolipram were much more sensitive to heat shock, reflecting an inhibition of enzymatic function.

The second type of pharmacological screen is applicable even when the mammalian gene encodes a protein of undetermined function, and, thus, cannot be assayed by a biochemical activity. In this method, agents to be tested are applied or introduced directly

to the genetically altered microbial host expressing the mammalian protein. Agents capable of inhibiting the mammalian gene or gene product are identified by their ability to reverse the phenotype originally corrected by expression of the mammalian protein in the altered host.

This procedure has been used for mammalian cDNAs encoding cyclic nucleotide phosphodiesterases and a yeast containing RAS2^{val19} as the host strain. When the rat DPD gene is introduced into the heat shock sensitive host and expressed, the host strain becomes heat shock resistant. When the now-resistant cells are incubated in Rolipram, they become heat shock sensitive again, indicating that Rolipram inhibits the activity of the rat DPD gene product. This pharmacological screen does not require that the function of the DPD gene product be known. This same approach can be applied to assess other genes.

In addition, any other phenotype that is dependent on DPD phosphodiesterase activity should be affected by the presence of the inhibitory drug. The effect of a drug or agent can be assessed as described. Finally, in the most generalized case, inhibitory chemicals for proteins of unknown function, expressed from mammalian cDNAs in yeast can be discovered in a similar way. This approach depends only on the phenotype consequent to expression of the protein and not on knowledge of its function.

For example, tyrosine kinases comprise a very large and diverse superfamily of proteins. They are important in regulation of cell growth. Certain tyrosine kinases are expressed ubiquitously in cells. Other tyrosine kinases display tissue specific distribution. Truly specific inhibitors of such tyrosine kinases could thus be expected to have specific and desirable therapeutic effects without unwanted side effects. For example, specific inhibitors of the PDGF

receptor-tyrosine kinase could be expected to retard the growth of atherosclerotic plaques or retard scar formation; specific inhibitors of the lck tyrosine kinase, which mediates signals from the CD4 and CD8 T-cell receptors, could be expected to be anti-inflammatory without being cytotoxic.

It is probable that yeast can be used to screen pharmacological agents for inhibition of specific tyrosine kinases. Brugge et al., Mol. Cell. Biol., 7:2180-2187 (1987) demonstrated that expression of the avian v-src gene in the yeast S. cerevisiae inhibits growth. This viral gene encodes a tyrosine specific protein kinase that closely resembles the cellular src genes that are expressed ubiquitously in mammalian and avian cells. If this is a general property of active mammalian tyrosine kinases expressed in yeast, then the following design for a pharmacological screen would be expected to be effective.

A specific mammalian tyrosine kinase cDNA gene can thus be inserted in a yeast shuttle vector such that it is under the control of an inducible yeast promoter, such as the GAL10 promoter which is inducible in the presence of galactose and in the absence of glucose. Introduction of this vector into a yeast cell can be anticipated to render that cell unable to grow in induction medium (containing galactose in the absence of glucose), since under such conditions the mammalian tyrosine kinase would be expressed to the detriment of the cell. In the presence of an inhibitor of the tyrosine kinase, such cells would thrive on induction medium. This provides a simple screen for pharmacological agents that inhibit mammalian tyrosine kinases. False positives would include agents that blocked induction of the expression of kinase. Such false positives could be distinguished by the failure of the mammalian kinase to be induced, which can be determined by quantitation with specific antibodies.

While the present invention has been described in terms of specific illustrative methods and materials, it is understood that modifications and variations thereof will occur to those skilled in the art upon consideration of the above detailed description. Consequently only such limitations as appear in the appended claims should be placed thereon.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: Cloning by Complementation and Related Processes

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(B) COMPUTER: IBM PC compatible
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AAGCGGCGGC

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GCGGCCGCTT

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2158 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1688

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
AGC TTG CGA ATC GTA AGA AAC AAT TTC ACC CTG CTG ACA AAC CTT CAC
Ser Leu Arg Ile Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His
  1               5                  10                  15

GGA GCA CCG AAC AAG AGG TCG CCA GCG GCT AGT CAG GCT CCA GTC ACC
Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr
             20                  25                  30
```

AGA GTC AGC CTG CAA GAA GAA TCA TAT CAG AAA CTA GCA ATG GAG ACG
Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr
35 40 45

CTG GAG GAA CTA GAC TGG TGC CTA GAC CAG CTA GAG ACC ATC CAG ACC
Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr
50 55 60

TAC CGC TCT GTC AGC GAG ATG GCT TCA AAC AAG TTC AAA AGG ATG CTG
Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu
65 70 75 80

AAC CGG GAG CTG ACA CAC CTC TCA GAG ATG AGC AGA TCA GGG AAC CAA
Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln
85 90 95

GTG TCT GAA TAC ATT TCG AAC ACG TTC TTA GAC AAG CAG AAC GAT GTG
Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val
100 105 110

GAA ATC CCA TCT CCC ACC CAG AAG GAC AGG GAG AAG AAG AAG AAG CAG
Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln
115 120 125

CAG CTC ATG ACC CAG ATA AGT GGA GTG AAG AAA CTG ATG CAC AGC TCA
Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser
130 135 140

AGC CTG AAC AAC ACA AGC ATC TCA CGC TTT GGA GTC AAC ACG GAA AAT
Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn
145 150 155 160

GAG GAT CAT CTA GCC AAG GAG CTG GAA GAC CTG AAC AAA TGG GGC CTT
Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu
165 170 175

AAC ATC TTC AAC GTG GCT GGG TAC TCC CAT AAT CGG CCC CTC ACA TGC
Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys
180 185 190

ATC ATG TAC GCC ATT TTC CAG GAA AGA GAC CTT CTA AAG ACG TTT AAA
Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys
195 200 205

ATC TCC TCC GAC ACC TTC GTA ACC TAC ATG ATG ACT TTA GAA GAC CAT
Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His
210 215 220

TAC CAT TCT GAT GTG GCG TAT CAC AAC AGC CTG CAC GCT GCT GAC GTG
Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val
225 230 235 240

```
GCC CAG TCA ACG CAC GTT CTC CTC TCT ACG CCA GCA CTG GAT GCT GTC
Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val
                245                 250                 255

TTC ACA GAC CTG GAA ATC CTG GCT GCC ATT TTT GCA GCT GCC ATC CAT
Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His
            260                 265                 270

GAT GTT GAT CAT CCT GGA GTC TCC AAT CAG TTT CTC ATC AAT ACA AAT
Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn
        275                 280                 285

TCC GAA CTT GCT TTG ATG TAT AAT GAC GAA TCT GTG CTG GAA AAC CAT
Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His
    290                 295                 300

CAC CTC GCT GTG GGA TTC AAG CTC CTT CAA GAG GAA CAT TGC GAC ATC
His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile
305                 310                 315                 320

TTT CAG AAT CTT ACC AAG AAG CAA CGC CAG ACA CTC AGG AAA ATG GTG
Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val
                325                 330                 335

ATT GAC ATG GTG TTA GCA ACT GAT ATG TCC AAG CAC ATG AGC CTC CTG
Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu
            340                 345                 350

GCT GAC CTT AAA ACG ATG GTA GAA ACC AAA AAG GTG ACG AGC TCC GGT
Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly
        355                 360                 365

GTT CTC CTC CTG GAC AAC TAT ACT GAC CGG ATA CAG GTT CTT CGC AAC
Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn
    370                 375                 380

ATG GTA CAT TGT GCA GAC CTG AGC AAC CCT ACC AAG TCC TTG GAG TTG
Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu
385                 390                 395                 400

TAT CGG CAA TGG ACT GAT CGC ATC ATG GAG GAG TTT TTC CAA CAG GGA
Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly
                405                 410                 415

GAC AAA GAA CGG GAG AGG GGA ATG GAG ATT AGC CCA ATG TGT GAT AAA
Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys
            420                 425                 430

CAC ACA GCT TCT GTG GAA AAG TCC CAG GTT GGT TTC ATT GAC TAC ATT
His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile
        435                 440                 445
```

```
GTC CAT CCA TTG TGG GAG ACC TGG GCA GAC CTG GTT CAG CCT GAT GCT
Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala
    450                 455                 460

CAA GAC ATT TTG GAC ACA CTA GAA GAT AAC AGG AAC TGG TAC CAG AGT
Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser
465                 470                 475                 480

ATG ATT CCC CAG AGC CCC TCT CCA CCA CTG GAC GAG AGG AGC AGG GAC
Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp
                485                 490                 495

TGC CAA GGC CTT ATG GAG AAG TTT CAG TTC GAA CTG ACC CTT GAA GAA
Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu
            500                 505                 510

GAG GAT TCT GAA GGA CCG GAA AAG GAG GGA GAA GGC CCC AAC TAT TTC
Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe
        515                 520                 525

AGC AGC ACA AAG ACA CTT TGT GTG ATC GAT CCA GAG AAC AGG GAT TCT
Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser
    530                 535                 540

CTG GAA GAG ACT GAC ATA GAC ATT GCC ACA GAA GAC AAG TCT CTG ATC
Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile
545                 550                 555                 560

GAC ACA TA ATCTCCCTCT GTGTGGAGGT GAACATTCTA TCCTTGACGA GCATGCCAGC
Asp Thr

TGAGTGGTAG GGCCCACCTA CCAGAGCCAA GGCCTGCACA AAACAAAGGC CACCTGGCTT

TGCAGTTACT TGAGTTTGGA GCCAGAATGC AAGGCCGTGA AGCAAATAGC AGTTCCGTGC

TGCCTTGCCT TGCCGGCGAG CTTGGCGAGA CCCGCAGCTG TAGTAGAAGC CAGTTCCCAG

CACAGCTAAA TGGCTTGAAA ACAGAGGACA GAAAGCTGAG AGATTGCTCT GCAATAGGTG

TTGAGGGGCT GTCCCGACAG GTGACTGAAC TCACTAACAA CTTCATCTAT AAATCTCACC

CATCCTGTTG TCTGCCAACC TGTGTGCCTT TTTTGTAAAA TGTTTTCGTG TCTTTGAAAT

GCCTGTTGAA TATCTAGAGT TTAGTACCTC CTTCTACAAA CTTTTTTGAG TCTTTCTGGG
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 562 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Ser Leu Arg Ile Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His
 1               5                  10                  15

Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr
            20                  25                  30

Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr
        35                  40                  45

Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr
    50                  55                  60

Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu
65                  70                  75                  80

Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln
                85                  90                  95

Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val
            100                 105                 110

Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln
        115                 120                 125

Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser
    130                 135                 140

Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn
145                 150                 155                 160

Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu
                165                 170                 175

Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys
            180                 185                 190

Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys
        195                 200                 205

Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His
    210                 215                 220

Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val
225                 230                 235                 240
```

```
Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val
                245                 250                 255

Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His
            260                 265                 270

Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn
        275                 280                 285

Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His
    290                 295                 300

His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile
305                 310                 315                 320

Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val
                325                 330                 335

Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu
            340                 345                 350

Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly
        355                 360                 365

Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn
    370                 375                 380

Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu
385                 390                 395                 400

Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly
                405                 410                 415

Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys
            420                 425                 430

His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile
        435                 440                 445

Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala
    450                 455                 460

Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser
465                 470                 475                 480

Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp
                485                 490                 495

Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu
            500                 505                 510

Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe
```

515 520 525

Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser
530 535 540

Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile
545 550 555 560

Asp Thr

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACCCTGCTG ACAAACCT

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

ATGGAGACGC TGGAGGAA

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATACGCCACA TCAGAATG

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TACCAGAGTA TGATTCCC

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GTGTCGATCA GAGACTTG

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GCACACAGGT TGGCAGAC

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1299 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1299

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
GGC CGC ATT GCC GAC CCG GCC CGT AGT GTG GAA GCA GCT TCA GCT CAA
Gly Arg Ile Ala Asp Pro Ala Arg Ser Val Glu Ala Ala Ser Ala Gln
  1               5                  10                  15

AGA TTA GAA CGA CTC CGA AAA GAG AGA CAA AAC CAG ATC AAA TGC AAA
Arg Leu Glu Arg Leu Arg Lys Glu Arg Gln Asn Gln Ile Lys Cys Lys
             20                  25                  30

AAT ATT CAG TGG AAA GAA AGA AAT TCT AAG CAA TCA GCC CAG GAG TTA
Asn Ile Gln Trp Lys Glu Arg Asn Ser Lys Gln Ser Ala Gln Glu Leu
         35                  40                  45

AAG TCA CTG TTT GAA AAA AAA TCT CTC AAA GAG AAG CCT CCA ATT TCT
Lys Ser Leu Phe Glu Lys Lys Ser Leu Lys Glu Lys Pro Pro Ile Ser
     50                  55                  60

GGG AAG CAG TCG ATA TTA TCT GTA CGC CTA GAA CAG TGC CCT CTG CAG
Gly Lys Gln Ser Ile Leu Ser Val Arg Leu Glu Gln Cys Pro Leu Gln
 65                  70                  75                  80

CTG AAT AAC CCT TTT AAC GAG TAT TCC AAA TTT GAT GGC AAG GGT CAT
Leu Asn Asn Pro Phe Asn Glu Tyr Ser Lys Phe Asp Gly Lys Gly His
                 85                  90                  95

GTA GGT ACA ACA GCA ACC AAG AAG ATC GAT GTC TAC CTC CCT CTG CAC
Val Gly Thr Thr Ala Thr Lys Lys Ile Asp Val Tyr Leu Pro Leu His
            100                 105                 110

TCG AGC CAG GAC AGA CTG CTG CCA ATG ACC GTG GTG ACA ATG GCC AGC
Ser Ser Gln Asp Arg Leu Leu Pro Met Thr Val Val Thr Met Ala Ser
        115                 120                 125

GCC AGG GTG CAG GAC CTG ATC GGG CTC ATC TGC TGG CAG TAT ACA AGC
Ala Arg Val Gln Asp Leu Ile Gly Leu Ile Cys Trp Gln Tyr Thr Ser
    130                 135                 140

GAA GGA CGG GAG CCG AAG CTC AAT GAC AAT GTC AGT GCC TAC TGC CTG
```

```
Glu Gly Arg Glu Pro Lys Leu Asn Asp Asn Val Ser Ala Tyr Cys Leu
145                 150                 155                 160

CAT ATT GCT GAG GAT GAT GGG GAG GTG GAC ACC GAT TTC CCC CCG CTG
His Ile Ala Glu Asp Asp Gly Glu Val Asp Thr Asp Phe Pro Pro Leu
                165                 170                 175

GAT TCC AAT GAG CCC ATT CAT AAG TTT GGC TTC AGT ACT TTG GCC CTG
Asp Ser Asn Glu Pro Ile His Lys Phe Gly Phe Ser Thr Leu Ala Leu
            180                 185                 190

GTT GAA AAG TAC TCA TCT CCT GGT CTG ACA TCC AAA GAG TCA CTC TTT
Val Glu Lys Tyr Ser Ser Pro Gly Leu Thr Ser Lys Glu Ser Leu Phe
        195                 200                 205

GTT CGA ATA AAT GCT GCT CAT GGA TTC TCC CTT ATT CAG GTG GAC AAC
Val Arg Ile Asn Ala Ala His Gly Phe Ser Leu Ile Gln Val Asp Asn
    210                 215                 220

ACA AAG GTT ACC ATG AAG GAA ATC TTA CTG AAG GCA GTG AAG CGA AGA
Thr Lys Val Thr Met Lys Glu Ile Leu Leu Lys Ala Val Lys Arg Arg
225                 230                 235                 240

AAA GGA TCC CAG AAA GTT TCA GGC CCT CAG TAC CGC CTG GAG AAG CAG
Lys Gly Ser Gln Lys Val Ser Gly Pro Gln Tyr Arg Leu Glu Lys Gln
                245                 250                 255

AGC GAG CCC AAT GTC GCC GTT GAC CTG GAC AGC ACT TTG GAG AGC CAG
Ser Glu Pro Asn Val Ala Val Asp Leu Asp Ser Thr Leu Glu Ser Gln
            260                 265                 270

AGC GCA TGG GAG TTC TGC CTG GTC CGC GAG AAC AGT TCA AGG GCA GAC
Ser Ala Trp Glu Phe Cys Leu Val Arg Glu Asn Ser Ser Arg Ala Asp
        275                 280                 285

GGG GTT TTT GAG GAG GAT TCG CAA ATT GAC ATA GCC ACA GTA CAG GAT
Gly Val Phe Glu Glu Asp Ser Gln Ile Asp Ile Ala Thr Val Gln Asp
    290                 295                 300

ATG CTT AGC AGC CAC CAT TAC AAG TCA TTC AAA GTC AGC ATG ATC CAC
Met Leu Ser Ser His His Tyr Lys Ser Phe Lys Val Ser Met Ile His
305                 310                 315                 320

AGA CTG CGA TTC ACA ACC GAC GTA CAG CTA GGT ATC TCT GGA GAC AAA
Arg Leu Arg Phe Thr Thr Asp Val Gln Leu Gly Ile Ser Gly Asp Lys
                325                 330                 335

GTA GAG ATA GAC CCT GTT ACG AAT CAG AAA GCC AGC ACT AAG TTT TGG
Val Glu Ile Asp Pro Val Thr Asn Gln Lys Ala Ser Thr Lys Phe Trp
            340                 345                 350

ATT AAG CAG AAA CCC ATC TCA ATC GAT TCC GAC CTG CTC TGT GCC TGT
```

Ile Lys Gln Lys Pro Ile Ser Ile Asp Ser Asp Leu Leu Cys Ala Cys
355 360 365

GAC CTT GCT GAA GAG AAA AGC CCC AGT CAC GCA ATA TTT AAA CTC ACG
Asp Leu Ala Glu Glu Lys Ser Pro Ser His Ala Ile Phe Lys Leu Thr
370 375 380

TAT CTA AGC AAT CAC GAC TAT AAA CAC CTC TAC TTT GAA TCG GAC GCT
Tyr Leu Ser Asn His Asp Tyr Lys His Leu Tyr Phe Glu Ser Asp Ala
385 390 395 400

GCT ACC GTC AAT GAA ATT GTG CTC AAG GTT AAC TAC ATC CTG GAA TCG
Ala Thr Val Asn Glu Ile Val Leu Lys Val Asn Tyr Ile Leu Glu Ser
405 410 415

CGA GCT AGC ACT GCC CGG GCT GAC TAC TTT GCT CAA AAA AAA AGC GGC
Arg Ala Ser Thr Ala Arg Ala Asp Tyr Phe Ala Gln Lys Lys Ser Gly
420 425 430

CGC
Arg

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 433 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gly Arg Ile Ala Asp Pro Ala Arg Ser Val Glu Ala Ala Ser Ala Gln
1 5 10 15

Arg Leu Glu Arg Leu Arg Lys Glu Arg Gln Asn Gln Ile Lys Cys Lys
20 25 30

Asn Ile Gln Trp Lys Glu Arg Asn Ser Lys Gln Ser Ala Gln Glu Leu
35 40 45

Lys Ser Leu Phe Glu Lys Lys Ser Leu Lys Glu Lys Pro Pro Ile Ser
50 55 60

Gly Lys Gln Ser Ile Leu Ser Val Arg Leu Glu Gln Cys Pro Leu Gln
65 70 75 80

Leu Asn Asn Pro Phe Asn Glu Tyr Ser Lys Phe Asp Gly Lys Gly His
85 90 95

Val Gly Thr Thr Ala Thr Lys Lys Ile Asp Val Tyr Leu Pro Leu His
100 105 110

Ser Ser Gln Asp Arg Leu Leu Pro Met Thr Val Val Thr Met Ala Ser
115 120 125

Ala Arg Val Gln Asp Leu Ile Gly Leu Ile Cys Trp Gln Tyr Thr Ser
130 135 140

Glu Gly Arg Glu Pro Lys Leu Asn Asp Asn Val Ser Ala Tyr Cys Leu
145 150 155 160

His Ile Ala Glu Asp Asp Gly Glu Val Asp Thr Asp Phe Pro Pro Leu
165 170 175

Asp Ser Asn Glu Pro Ile His Lys Phe Gly Phe Ser Thr Leu Ala Leu
180 185 190

Val Glu Lys Tyr Ser Ser Pro Gly Leu Thr Ser Lys Glu Ser Leu Phe
195 200 205

Val Arg Ile Asn Ala Ala His Gly Phe Ser Leu Ile Gln Val Asp Asn
210 215 220

Thr Lys Val Thr Met Lys Glu Ile Leu Leu Lys Ala Val Lys Arg Arg
225 230 235 240

Lys Gly Ser Gln Lys Val Ser Gly Pro Gln Tyr Arg Leu Glu Lys Gln
245 250 255

Ser Glu Pro Asn Val Ala Val Asp Leu Asp Ser Thr Leu Glu Ser Gln
260 265 270

Ser Ala Trp Glu Phe Cys Leu Val Arg Glu Asn Ser Ser Arg Ala Asp
275 280 285

Gly Val Phe Glu Glu Asp Ser Gln Ile Asp Ile Ala Thr Val Gln Asp
290 295 300

Met Leu Ser Ser His His Tyr Lys Ser Phe Lys Val Ser Met Ile His
305 310 315 320

Arg Leu Arg Phe Thr Thr Asp Val Gln Leu Gly Ile Ser Gly Asp Lys
325 330 335

Val Glu Ile Asp Pro Val Thr Asn Gln Lys Ala Ser Thr Lys Phe Trp
340 345 350

Ile Lys Gln Lys Pro Ile Ser Ile Asp Ser Asp Leu Leu Cys Ala Cys
355 360 365

```
Asp Leu Ala Glu Glu Lys Ser Pro Ser His Ala Ile Phe Lys Leu Thr
    370                 375                 380

Tyr Leu Ser Asn His Asp Tyr Lys His Leu Tyr Phe Glu Ser Asp Ala
385                 390                 395                     400

Ala Thr Val Asn Glu Ile Val Leu Lys Val Asn Tyr Ile Leu Glu Ser
                405                 410                 415

Arg Ala Ser Thr Ala Arg Ala Asp Tyr Phe Ala Gln Lys Lys Ser Gly
            420                 425                 430

Arg
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1721 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 60..1274

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
AAGCTTGCGG CCGCATTGGG TACCGCGTGC CAGCAGGCAG TGGCCCTAGC CTTCCGCCT

ATG CCC TCC CTC CAA GAG GTG GAC TGC GGC TCC CCC AGC AGC TCC GAG
Met Pro Ser Leu Gln Glu Val Asp Cys Gly Ser Pro Ser Ser Ser Glu
  1               5                  10                  15

GAG GAG GGG GTG CCA GGG TCC CGG GGG AGC CCA GCG ACC TCA CCC CAC
Glu Glu Gly Val Pro Gly Ser Arg Gly Ser Pro Ala Thr Ser Pro His
             20                  25                  30

CTG GGC CGC CGA CGA CCT CTG CTT CGG TCC ATG AGC GCC GCC TTC TGC
Leu Gly Arg Arg Arg Pro Leu Leu Arg Ser Met Ser Ala Ala Phe Cys
         35                  40                  45

TCC CTA CTG GCA CCG GAG CGG CAG GTG GGC CGG GCT GCG GCA GCA CTG
Ser Leu Leu Ala Pro Glu Arg Gln Val Gly Arg Ala Ala Ala Ala Leu
     50                  55                  60

ATG CAG GAC CGA CAC ACA GCC GCG GGC CAG CTG GTG CAG GAC CTA CTG
```

```
Met Gln Asp Arg His Thr Ala Ala Gly Gln Leu Val Gln Asp Leu Leu
65                  70                  75                  80

ACC CAG GTG CGG GAT GGG CAG AGG CCC CAG GAG CTC GAG GGC ATC CGT
Thr Gln Val Arg Asp Gly Gln Arg Pro Gln Glu Leu Glu Gly Ile Arg
                85                  90                  95

CAG GCG CTG AGC CGG GCC CGG GCC ATG CTG AGT GCG GAG CTG GGC CCT
Gln Ala Leu Ser Arg Ala Arg Ala Met Leu Ser Ala Glu Leu Gly Pro
            100                 105                 110

GAG AAG CTC GTG TCG CCT AAG AGG CTG GAA CAT GTC CTG GAG AAG TCA
Glu Lys Leu Val Ser Pro Lys Arg Leu Glu His Val Leu Glu Lys Ser
        115                 120                 125

TTG CAT TGC TCT GTG CTC AAG CCT CTC CGG CCC ATC CTG GCA GCC CGC
Leu His Cys Ser Val Leu Lys Pro Leu Arg Pro Ile Leu Ala Ala Arg
    130                 135                 140

CTG CGG CGC CGG CTT GCC GCA GAC GGC TCC CTG GGC CGC CTA GCT GAG
Leu Arg Arg Arg Leu Ala Ala Asp Gly Ser Leu Gly Arg Leu Ala Glu
145                 150                 155                 160

GGC CTC CGC CTG GCC CGG GCC CAG GGC CCC GGA GCC TTC GGG TCC CAC
Gly Leu Arg Leu Ala Arg Ala Gln Gly Pro Gly Ala Phe Gly Ser His
                165                 170                 175

CTG AGC CTG CCC TCC CCA GTA GAG TTG GAG CAA GTG CGC CAG AAG CTG
Leu Ser Leu Pro Ser Pro Val Glu Leu Glu Gln Val Arg Gln Lys Leu
            180                 185                 190

CTG CAG CTC GTC CGC ACC TAC TCA CCC AGC GCC CAG GTC AAG CGG CTC
Leu Gln Leu Val Arg Thr Tyr Ser Pro Ser Ala Gln Val Lys Arg Leu
        195                 200                 205

CTG CAG GCC TGC AAG CTG CTC TAC ATG GCC CTG AGG ACC CAG GAA GGG
Leu Gln Ala Cys Lys Leu Leu Tyr Met Ala Leu Arg Thr Gln Glu Gly
    210                 215                 220

GAG GGC TCG GGT GCC GAC GGG TTC CTG CCT CTG CTG AGC CTC GTC TTG
Glu Gly Ser Gly Ala Asp Gly Phe Leu Pro Leu Leu Ser Leu Val Leu
225                 230                 235                 240

GCC CAC TGT GAC CTT CCT GAG CTG CTG CTG GAG GCC GAG TAC ATG TCG
Ala His Cys Asp Leu Pro Glu Leu Leu Leu Glu Ala Glu Tyr Met Ser
                245                 250                 255

GAG CTG CTG GAG CCC AGC CTG CTT ACT GGA GAG GGT GGC TAC TAC CTG
Glu Leu Leu Glu Pro Ser Leu Leu Thr Gly Glu Gly Gly Tyr Tyr Leu
            260                 265                 270

ACC AGC CTC TCT GCC AGC CTG GCC CTG CTG AGT GGC CTG GGT CAG GCC
```

Thr Ser Leu Ser Ala Ser Leu Ala Leu Leu Ser Gly Leu Gly Gln Ala
275 280 285

CAC ACC CTC CCA CTG AGC CCC GTG CAG GAG CTA CGG CGC TCC CTC AGC
His Thr Leu Pro Leu Ser Pro Val Gln Glu Leu Arg Arg Ser Leu Ser
290 295 300

CTC TGG GAG CAG CGC CGC CTG CCT GCC ACC CAC TGC TTC CAG CAC CTC
Leu Trp Glu Gln Arg Arg Leu Pro Ala Thr His Cys Phe Gln His Leu
305 310 315 320

CTC CGA GTA GCC TAT CAG GAT CCC AGC AGT GGC TGC ACC TCC AAG ACC
Leu Arg Val Ala Tyr Gln Asp Pro Ser Ser Gly Cys Thr Ser Lys Thr
325 330 335

CTG GCC GTG CCC CCA GAG GCC TCG ATT GCC ACC CTG AAC CAG CTC TGT
Leu Ala Val Pro Pro Glu Ala Ser Ile Ala Thr Leu Asn Gln Leu Cys
340 345 350

GCC ACC AAG TTC CGA GTG ACC CAG CCC AAC ACT TTT GGC CTC TTC CTG
Ala Thr Lys Phe Arg Val Thr Gln Pro Asn Thr Phe Gly Leu Phe Leu
355 360 365

TAC AAG GAG CAG GGC TAC CAC CGC CTG CCC CCT GGG CCC TGG CCC ACA
Tyr Lys Glu Gln Gly Tyr His Arg Leu Pro Pro Gly Pro Trp Pro Thr
370 375 380

GGC TGC CCA CCA CTG GCT ACC TCG TCT ACC GCC GGG CAG AGT GGC CTG
Gly Cys Pro Pro Leu Ala Thr Ser Ser Thr Ala Gly Gln Ser Gly Leu
385 390 395 400

AGA CCC AGG GGG CTG TGACAGAGGA GGAGGGCAGT GGGCAGTCAG AGGCAAGAAG
Arg Pro Arg Gly Leu
405

CAGAGGGGAG GAGCAAGGGT GCCAGGGAGA TGGGGATGCT GGGGTCAAAG CCAGCCCCAG

GGACATTCGG GAACAGTCTG AGACAACTGC TGAAGGGGGC CAGGGTCAAG CCCAGGAAGG

CCCTGCTCAG CCAGGGGAAC CAGAGGCAGA GGGAAGCCGG GCAGCAGAGG AGTAGCTTGA

AGTGGCCAGA AGGGTCATTC GGGGCGGGAG ACCCTGAGCC TGCTGAGAAA TCCTTTTAGC

GCCAGCAAGC CCCACCCAGG GCCCTGTCCT GTGTCTGCCA CCACCTTTGT CTGATACTTG

TTTCCAGGGA AGCTGGGGGA ACTGCCACAT CTGAGGAACT GGAATAAAGA TGAGGGGCCT

TCGGGGGCCA ATGCGGCCGC CGCGGCCTTT TTGGCCAGCT CGAATTC

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 405 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Met Pro Ser Leu Gln Glu Val Asp Cys Gly Ser Pro Ser Ser Ser Glu
  1               5                  10                  15

Glu Glu Gly Val Pro Gly Ser Arg Gly Ser Pro Ala Thr Ser Pro His
             20                  25                  30

Leu Gly Arg Arg Arg Pro Leu Leu Arg Ser Met Ser Ala Ala Phe Cys
         35                  40                  45

Ser Leu Leu Ala Pro Glu Arg Gln Val Gly Arg Ala Ala Ala Ala Leu
     50                  55                  60

Met Gln Asp Arg His Thr Ala Ala Gly Gln Leu Val Gln Asp Leu Leu
 65                  70                  75                  80

Thr Gln Val Arg Asp Gly Gln Arg Pro Gln Glu Leu Glu Gly Ile Arg
                 85                  90                  95

Gln Ala Leu Ser Arg Ala Arg Ala Met Leu Ser Ala Glu Leu Gly Pro
            100                 105                 110

Glu Lys Leu Val Ser Pro Lys Arg Leu Glu His Val Leu Glu Lys Ser
        115                 120                 125

Leu His Cys Ser Val Leu Lys Pro Leu Arg Pro Ile Leu Ala Ala Arg
    130                 135                 140

Leu Arg Arg Arg Leu Ala Ala Asp Gly Ser Leu Gly Arg Leu Ala Glu
145                 150                 155                 160

Gly Leu Arg Leu Ala Arg Ala Gln Gly Pro Gly Ala Phe Gly Ser His
                165                 170                 175

Leu Ser Leu Pro Ser Pro Val Glu Leu Glu Gln Val Arg Gln Lys Leu
            180                 185                 190

Leu Gln Leu Val Arg Thr Tyr Ser Pro Ser Ala Gln Val Lys Arg Leu
        195                 200                 205

Leu Gln Ala Cys Lys Leu Leu Tyr Met Ala Leu Arg Thr Gln Glu Gly
    210                 215                 220

Glu Gly Ser Gly Ala Asp Gly Phe Leu Pro Leu Leu Ser Leu Val Leu
```

225 230 235 240

Ala His Cys Asp Leu Pro Glu Leu Leu Leu Glu Ala Glu Tyr Met Ser
245 250 255

Glu Leu Leu Glu Pro Ser Leu Leu Thr Gly Glu Gly Gly Tyr Tyr Leu
260 265 270

Thr Ser Leu Ser Ala Ser Leu Ala Leu Leu Ser Gly Leu Gly Gln Ala
275 280 285

His Thr Leu Pro Leu Ser Pro Val Gln Glu Leu Arg Arg Ser Leu Ser
290 295 300

Leu Trp Glu Gln Arg Arg Leu Pro Ala Thr His Cys Phe Gln His Leu
305 310 315 320

Leu Arg Val Ala Tyr Gln Asp Pro Ser Ser Gly Cys Thr Ser Lys Thr
325 330 335

Leu Ala Val Pro Pro Glu Ala Ser Ile Ala Thr Leu Asn Gln Leu Cys
340 345 350

Ala Thr Lys Phe Arg Val Thr Gln Pro Asn Thr Phe Gly Leu Phe Leu
355 360 365

Tyr Lys Glu Gln Gly Tyr His Arg Leu Pro Pro Gly Pro Trp Pro Thr
370 375 380

Gly Cys Pro Pro Leu Ala Thr Ser Ser Thr Ala Gly Gln Ser Gly Leu
385 390 395 400

Arg Pro Arg Gly Leu
405

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1829 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..1421

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

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GCGGCCGCGG CCGGCAGCGG CTGAGCGAC ATG AGC ATT TCT ACT TCC TCC TCC
                                Met Ser Ile Ser Thr Ser Ser Ser
                                 1               5

GAC TCG CTG GAG TTC GAC CGG AGC ATG CCT CTG TTT GGC TAC GAG GCG
Asp Ser Leu Glu Phe Asp Arg Ser Met Pro Leu Phe Gly Tyr Glu Ala
     10                  15                  20

GAC ACC AAC AGC AGC CTG GAG GAC TAC GAG GGG GAA AGT GAC CAA GAG
Asp Thr Asn Ser Ser Leu Glu Asp Tyr Glu Gly Glu Ser Asp Gln Glu
 25                  30                  35                  40

ACC ATG GCG CCC CCC ATC AAG TCC AAA AAG AAA AGG AGC AGC TCC TTC
Thr Met Ala Pro Pro Ile Lys Ser Lys Lys Lys Arg Ser Ser Ser Phe
                 45                  50                  55

GTG CTG CCC AAG CTC GTC AAG TCC CAG CTG CAG AAG GTG AGC GGG GTG
Val Leu Pro Lys Leu Val Lys Ser Gln Leu Gln Lys Val Ser Gly Val
             60                  65                  70

TTC AGC TCC TTC ATG ACC CCG GAG AAG CGG ATG GTC CGC AGG ATC GCC
Phe Ser Ser Phe Met Thr Pro Glu Lys Arg Met Val Arg Arg Ile Ala
         75                  80                  85

GAG CTT TCC CGG GAC AAA TGC ACC TAC TTC GGG TGC TTA GTG CAG GAC
Glu Leu Ser Arg Asp Lys Cys Thr Tyr Phe Gly Cys Leu Val Gln Asp
     90                  95                 100

TAC GTG AGC TTC CTG CAG GAG AAC AAG GAG TGC CAC GTG TCC AGC ACC
Tyr Val Ser Phe Leu Gln Glu Asn Lys Glu Cys His Val Ser Ser Thr
105                 110                 115                 120

GAC ATG CTG CAG ACC ATC CGG CAG TTC ATG ACC CAG GTC AAG AAC TAT
Asp Met Leu Gln Thr Ile Arg Gln Phe Met Thr Gln Val Lys Asn Tyr
                125                 130                 135

TTG TCT CAG AGC TCG GAG CTG GAC CCC CCC ATC GAG TCG CTG ATC CCT
Leu Ser Gln Ser Ser Glu Leu Asp Pro Pro Ile Glu Ser Leu Ile Pro
            140                 145                 150

GAA GAC CAA ATA GAT GTG GTG CTG GAA AAA GCC ATG CAC AAG TGC ATC
Glu Asp Gln Ile Asp Val Val Leu Glu Lys Ala Met His Lys Cys Ile
        155                 160                 165

TTG AAG CCC CTC AAG GGG CAC GTG GAG GCC ATG CTG AAG GAC TTT CAC
Leu Lys Pro Leu Lys Gly His Val Glu Ala Met Leu Lys Asp Phe His
    170                 175                 180

ATG GCC GAT GGC TCA TGG AAG CAA CTC AAG GAG AAC CTG CAG CTT GTG
Met Ala Asp Gly Ser Trp Lys Gln Leu Lys Glu Asn Leu Gln Leu Val
185                 190                 195                 200
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CGG CAG AGG AAT CCG CAG GAG CTG GGG GTC TTC GCC CCG ACC CCT GAT
Arg Gln Arg Asn Pro Gln Glu Leu Gly Val Phe Ala Pro Thr Pro Asp
                205                 210                 215

TTT GTG GAT GTG GAG AAA ATC AAA GTC AAG TTC ATG ACC ATG CAG AAG
Phe Val Asp Val Glu Lys Ile Lys Val Lys Phe Met Thr Met Gln Lys
            220                 225                 230

ATG TAT TCG CCG GAA AAG AAG GTC ATG CTG CTG CTG CGG GTC TGC AAG
Met Tyr Ser Pro Glu Lys Lys Val Met Leu Leu Leu Arg Val Cys Lys
        235                 240                 245

CTC ATT TAC ACG GTC ATG GAG AAC AAC TCA GGG AGG ATG TAT GGC GCT
Leu Ile Tyr Thr Val Met Glu Asn Asn Ser Gly Arg Met Tyr Gly Ala
    250                 255                 260

GAT GAC TTC TTG CCA GTC CTG ACC TAT GTC ATA GCC CAG TGT GAC ATG
Asp Asp Phe Leu Pro Val Leu Thr Tyr Val Ile Ala Gln Cys Asp Met
265                 270                 275                     280

CTT GAA TTG GAC ACT GAA ATC GAG TAC ATG ATG GAG CTC CTA GAC CCA
Leu Glu Leu Asp Thr Glu Ile Glu Tyr Met Met Glu Leu Leu Asp Pro
                285                 290                 295

TCG CTG TTA CAT GGA GAA GGA GGC TAT TAC TTG ACA AGC GCA TAT GGA
Ser Leu Leu His Gly Glu Gly Gly Tyr Tyr Leu Thr Ser Ala Tyr Gly
            300                 305                 310

GCA CTT TCT CTG ATA AAG AAT TTC CAA GAA GAA CAA GCA GCG CGA CTG
Ala Leu Ser Leu Ile Lys Asn Phe Gln Glu Glu Gln Ala Ala Arg Leu
        315                 320                 325

CTC AGC TCA GAA ACC AGA GAC ACC CTG AGG CAG TGG CAC AAA CGG AGA
Leu Ser Ser Glu Thr Arg Asp Thr Leu Arg Gln Trp His Lys Arg Arg
    330                 335                 340

ACC ACC AAC CGG ACC ATC CCC TCT GTG GAC GAC TTC CAG AAT TAC CTC
Thr Thr Asn Arg Thr Ile Pro Ser Val Asp Asp Phe Gln Asn Tyr Leu
345                 350                 355                     360

CGA GTT GCA TTT CAG GAG GTC AAC AGT GGT TGC ACA GGA AAG ACC CTC
Arg Val Ala Phe Gln Glu Val Asn Ser Gly Cys Thr Gly Lys Thr Leu
                365                 370                 375

CTT GTG AGA CCT TAC ATC ACC ACT GAG GAT GTG TGT CAG ATC TGC GCT
Leu Val Arg Pro Tyr Ile Thr Thr Glu Asp Val Cys Gln Ile Cys Ala
            380                 385                 390

GAG AAG TTC AAG GTG GGG GAC CCT GAG GAG TAC AGC CTC TTT CTC TTC
Glu Lys Phe Lys Val Gly Asp Pro Glu Glu Tyr Ser Leu Phe Leu Phe
        395                 400                 405
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GTT GAC GAG ACA TGG CAG CAG CTG GCA GAG GAC ACT TAC CCT CAA AAA
Val Asp Glu Thr Trp Gln Gln Leu Ala Glu Asp Thr Tyr Pro Gln Lys
410 415 420

ATC AAG GCG GAG CTG CAC AGC CGA CCA CAG CCC CAC ATC TTC CAC TTT
Ile Lys Ala Glu Leu His Ser Arg Pro Gln Pro His Ile Phe His Phe
425 430 435 440

GTC TAC AAA CGC ATC AAG AAC GAT CCT TAT GGC ATC ATT TTC CAG AAC
Val Tyr Lys Arg Ile Lys Asn Asp Pro Tyr Gly Ile Ile Phe Gln Asn
445 450 455

GGG GAA GAA GAC CTC ACC ACC TCC TAGAAGACAG GCGGGACTTC CCAGTGGTGC
Gly Glu Glu Asp Leu Thr Thr Ser
460

ATCCAAAGGG GAGCTGGAAG CCTTGCCTTC CCGCTTCTAC ATGCTTGAGC TTGAAAAGCA

GTCACCTCCT CGGGGACCCC TCAGTGTAGT GACTAAGCCA TCCACAGGCC AACTCGGCCA

AGGGCAACTT TAGCCACGCA AGGTAGCTGA GGTTTGTGAA ACAGTAGGAT TCTCTTTTGG

CAATGGAGAA TTGCATCTGA TGGTTCAAGT GTCCTGAGAT TGTTTGCTAC CTACCCCCAG

TCAGGTTCTA GGTTGGCTTA CAGGTATGTA TATGTGCAGA AGAAACACTT AAGATACAAG

TTCTTTTGAA TTCAACAGCA GATGCTTGCG ATGCAGTGCG TCAGGTGATT CTCACTCCTG

TGGATGGCTT CATCCCTG

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 464 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ser Ile Ser Thr Ser Ser Ser Asp Ser Leu Glu Phe Asp Arg Ser
1 5 10 15

Met Pro Leu Phe Gly Tyr Glu Ala Asp Thr Asn Ser Ser Leu Glu Asp
20 25 30

Tyr Glu Gly Glu Ser Asp Gln Glu Thr Met Ala Pro Pro Ile Lys Ser
35 40 45

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Lys Lys Lys Arg Ser Ser Ser Phe Val Leu Pro Lys Leu Val Lys Ser
     50                  55                  60

Gln Leu Gln Lys Val Ser Gly Val Phe Ser Ser Phe Met Thr Pro Glu
 65                  70                  75                  80

Lys Arg Met Val Arg Arg Ile Ala Glu Leu Ser Arg Asp Lys Cys Thr
                 85                  90                  95

Tyr Phe Gly Cys Leu Val Gln Asp Tyr Val Ser Phe Leu Gln Glu Asn
            100                 105                 110

Lys Glu Cys His Val Ser Ser Thr Asp Met Leu Gln Thr Ile Arg Gln
        115                 120                 125

Phe Met Thr Gln Val Lys Asn Tyr Leu Ser Gln Ser Ser Glu Leu Asp
    130                 135                 140

Pro Pro Ile Glu Ser Leu Ile Pro Glu Asp Gln Ile Asp Val Val Leu
145                 150                 155                 160

Glu Lys Ala Met His Lys Cys Ile Leu Lys Pro Leu Lys Gly His Val
                165                 170                 175

Glu Ala Met Leu Lys Asp Phe His Met Ala Asp Gly Ser Trp Lys Gln
            180                 185                 190

Leu Lys Glu Asn Leu Gln Leu Val Arg Gln Arg Asn Pro Gln Glu Leu
        195                 200                 205

Gly Val Phe Ala Pro Thr Pro Asp Phe Val Asp Val Glu Lys Ile Lys
    210                 215                 220

Val Lys Phe Met Thr Met Gln Lys Met Tyr Ser Pro Glu Lys Lys Val
225                 230                 235                 240

Met Leu Leu Leu Arg Val Cys Lys Leu Ile Tyr Thr Val Met Glu Asn
                245                 250                 255

Asn Ser Gly Arg Met Tyr Gly Ala Asp Asp Phe Leu Pro Val Leu Thr
            260                 265                 270

Tyr Val Ile Ala Gln Cys Asp Met Leu Glu Leu Asp Thr Glu Ile Glu
        275                 280                 285

Tyr Met Met Glu Leu Leu Asp Pro Ser Leu Leu His Gly Glu Gly Gly
    290                 295                 300

Tyr Tyr Leu Thr Ser Ala Tyr Gly Ala Leu Ser Leu Ile Lys Asn Phe
305                 310                 315                 320

Gln Glu Glu Gln Ala Ala Arg Leu Leu Ser Ser Glu Thr Arg Asp Thr
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325 330 335

Leu Arg Gln Trp His Lys Arg Arg Thr Thr Asn Arg Thr Ile Pro Ser
340 345 350

Val Asp Asp Phe Gln Asn Tyr Leu Arg Val Ala Phe Gln Glu Val Asn
355 360 365

Ser Gly Cys Thr Gly Lys Thr Leu Leu Val Arg Pro Tyr Ile Thr Thr
370 375 380

Glu Asp Val Cys Gln Ile Cys Ala Glu Lys Phe Lys Val Gly Asp Pro
385 390 395 400

Glu Glu Tyr Ser Leu Phe Leu Phe Val Asp Glu Thr Trp Gln Gln Leu
405 410 415

Ala Glu Asp Thr Tyr Pro Gln Lys Ile Lys Ala Glu Leu His Ser Arg
420 425 430

Pro Gln Pro His Ile Phe His Phe Val Tyr Lys Arg Ile Lys Asn Asp
435 440 445

Pro Tyr Gly Ile Ile Phe Gln Asn Gly Glu Glu Asp Leu Thr Thr Ser
450 455 460

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1299 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1299

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGC CGC ATT GCC GAC CCG GCC CGT AGT GTG GAA GCA GCT TCA GCT CAA
Gly Arg Ile Ala Asp Pro Ala Arg Ser Val Glu Ala Ala Ser Ala Gln
1 5 10 15

AGA TTA GAA CGA CTC CGA AAA GAG AGA CAA AAC CAG ATC AAA TGC AAA
Arg Leu Glu Arg Leu Arg Lys Glu Arg Gln Asn Gln Ile Lys Cys Lys
20 25 30

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AAT ATT CAG TGG AAA GAA AGA AAT TCT AAG CAA TCA GCC CAG GAG TTA
Asn Ile Gln Trp Lys Glu Arg Asn Ser Lys Gln Ser Ala Gln Glu Leu
         35                  40                  45

AAG TCA CTG TTT GAA AAA AAA TCT CTC AAA GAG AAG CCT CCA ATT TCT
Lys Ser Leu Phe Glu Lys Lys Ser Leu Lys Glu Lys Pro Pro Ile Ser
     50                  55                  60

GGG AAG CAG TCG ATA TTA TCT GTA CGC CTA GAA CAG TGC CCT CTG CAG
Gly Lys Gln Ser Ile Leu Ser Val Arg Leu Glu Gln Cys Pro Leu Gln
 65                  70                  75                  80

CTG AAT AAC CCT TTT AAC GAG TAT TCC AAA TTT GAT GGC AAG GGT CAT
Leu Asn Asn Pro Phe Asn Glu Tyr Ser Lys Phe Asp Gly Lys Gly His
                 85                  90                  95

GTA GGT ACA ACA GCA ACC AAG AAG ATC GAT GTC TAC CTC CCT CTG CAC
Val Gly Thr Thr Ala Thr Lys Lys Ile Asp Val Tyr Leu Pro Leu His
            100                 105                 110

TCG AGC CAG GAC AGA CTG CTG CCA ATG ACC GTG GTG ACA ATG GCC AGC
Ser Ser Gln Asp Arg Leu Leu Pro Met Thr Val Val Thr Met Ala Ser
        115                 120                 125

GCC AGG GTG CAG GAC CTG ATC GGG CTC ATC TGC TGG CAG TAT ACA AGC
Ala Arg Val Gln Asp Leu Ile Gly Leu Ile Cys Trp Gln Tyr Thr Ser
    130                 135                 140

GAA GGA CGG GAG CCG AAG CTC AAT GAC AAT GTC AGT GCC TAC TGC CTG
Glu Gly Arg Glu Pro Lys Leu Asn Asp Asn Val Ser Ala Tyr Cys Leu
145                 150                 155                 160

CAT ATT GCT GAG GAT GAT GGG GAG GTG GAC ACC GAT TTC CCC CCG CTG
His Ile Ala Glu Asp Asp Gly Glu Val Asp Thr Asp Phe Pro Pro Leu
                165                 170                 175

GAT TCC AAT GAG CCC ATT CAT AAG TTT GGC TTC AGT ACT TTG GCC CTG
Asp Ser Asn Glu Pro Ile His Lys Phe Gly Phe Ser Thr Leu Ala Leu
            180                 185                 190

GTT GAA AAG TAC TCA TCT CCT GGT CTG ACA TCC AAA GAG TCA CTC TTT
Val Glu Lys Tyr Ser Ser Pro Gly Leu Thr Ser Lys Glu Ser Leu Phe
        195                 200                 205

GTT CGA ATA AAT GCT GCT CAT GGA TTC TCC CTT ATT CAG GTG GAC AAC
Val Arg Ile Asn Ala Ala His Gly Phe Ser Leu Ile Gln Val Asp Asn
    210                 215                 220

ACA AAG GTT ACC ATG AAG GAA ATC TTA CTG AAG GCA GTG AAG CGA AGA
Thr Lys Val Thr Met Lys Glu Ile Leu Leu Lys Ala Val Lys Arg Arg
225                 230                 235                 240
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AAA GGA TCC CAG AAA GTT TCA GGC CCT CAG TAC CGC CTG GAG AAG CAG
Lys Gly Ser Gln Lys Val Ser Gly Pro Gln Tyr Arg Leu Glu Lys Gln
                245                 250                 255

AGC GAG CCC AAT GTC GCC GTT GAC CTG GAC AGC ACT TTG GAG AGC CAG
Ser Glu Pro Asn Val Ala Val Asp Leu Asp Ser Thr Leu Glu Ser Gln
            260                 265                 270

AGC GCA TGG GAG TTC TGC CTG GTC CGC GAG AAC AGT TCA AGG GCA GAC
Ser Ala Trp Glu Phe Cys Leu Val Arg Glu Asn Ser Ser Arg Ala Asp
        275                 280                 285

GGG GTT TTT GAG GAG GAT TCG CAA ATT GAC ATA GCC ACA GTA CAG GAT
Gly Val Phe Glu Glu Asp Ser Gln Ile Asp Ile Ala Thr Val Gln Asp
    290                 295                 300

ATG CTT AGC AGC CAC CAT TAC AAG TCA TTC AAA GTC AGC ATG ATC CAC
Met Leu Ser Ser His His Tyr Lys Ser Phe Lys Val Ser Met Ile His
305                 310                 315                 320

AGA CTG CGA TTC ACA ACC GAC GTA CAG CTA GGT ATC TCT GGA GAC AAA
Arg Leu Arg Phe Thr Thr Asp Val Gln Leu Gly Ile Ser Gly Asp Lys
                325                 330                 335

GTA GAG ATA GAC CCT GTT ACG AAT CAG AAA GCC AGC ACT AAG TTT TGG
Val Glu Ile Asp Pro Val Thr Asn Gln Lys Ala Ser Thr Lys Phe Trp
            340                 345                 350

ATT AAG CAG AAA CCC ATC TCA ATC GAT TCC GAC CTG CTC TGT GCC TGT
Ile Lys Gln Lys Pro Ile Ser Ile Asp Ser Asp Leu Leu Cys Ala Cys
        355                 360                 365

GAC CTT GCT GAA GAG AAA AGC CCC AGT CAC GCA ATA TTT AAA CTC ACG
Asp Leu Ala Glu Glu Lys Ser Pro Ser His Ala Ile Phe Lys Leu Thr
    370                 375                 380

TAT CTA AGC AAT CAC GAC TAT AAA CAC CTC TAC TTT GAA TCG GAC GCT
Tyr Leu Ser Asn His Asp Tyr Lys His Leu Tyr Phe Glu Ser Asp Ala
385                 390                 395                 400

GCT ACC GTC AAT GAA ATT GTG CTC AAG GTT AAC TAC ATC CTG GAA TCG
Ala Thr Val Asn Glu Ile Val Leu Lys Val Asn Tyr Ile Leu Glu Ser
                405                 410                 415

CGA GCT AGC ACT GCC CGG GCT GAC TAC TTT GCT CAA AAA AAA AGC GGC
Arg Ala Ser Thr Ala Arg Ala Asp Tyr Phe Ala Gln Lys Lys Ser Gly
            420                 425                 430

CGC
Arg
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 433 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Gly Arg Ile Ala Asp Pro Ala Arg Ser Val Glu Ala Ala Ser Ala Gln
 1               5                  10                  15

Arg Leu Glu Arg Leu Arg Lys Glu Arg Gln Asn Gln Ile Lys Cys Lys
            20                  25                  30

Asn Ile Gln Trp Lys Glu Arg Asn Ser Lys Gln Ser Ala Gln Glu Leu
        35                  40                  45

Lys Ser Leu Phe Glu Lys Lys Ser Leu Lys Glu Lys Pro Pro Ile Ser
    50                  55                  60

Gly Lys Gln Ser Ile Leu Ser Val Arg Leu Glu Gln Cys Pro Leu Gln
65                  70                  75                  80

Leu Asn Asn Pro Phe Asn Glu Tyr Ser Lys Phe Asp Gly Lys Gly His
                85                  90                  95

Val Gly Thr Thr Ala Thr Lys Lys Ile Asp Val Tyr Leu Pro Leu His
            100                 105                 110

Ser Ser Gln Asp Arg Leu Leu Pro Met Thr Val Val Thr Met Ala Ser
        115                 120                 125

Ala Arg Val Gln Asp Leu Ile Gly Leu Ile Cys Trp Gln Tyr Thr Ser
    130                 135                 140

Glu Gly Arg Glu Pro Lys Leu Asn Asp Asn Val Ser Ala Tyr Cys Leu
145                 150                 155                 160

His Ile Ala Glu Asp Asp Gly Glu Val Asp Thr Asp Phe Pro Pro Leu
                165                 170                 175

Asp Ser Asn Glu Pro Ile His Lys Phe Gly Phe Ser Thr Leu Ala Leu
            180                 185                 190

Val Glu Lys Tyr Ser Ser Pro Gly Leu Thr Ser Lys Glu Ser Leu Phe
        195                 200                 205
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Val Arg Ile Asn Ala Ala His Gly Phe Ser Leu Ile Gln Val Asp Asn
    210                 215                 220

Thr Lys Val Thr Met Lys Glu Ile Leu Leu Lys Ala Val Lys Arg Arg
225                 230                 235                 240

Lys Gly Ser Gln Lys Val Ser Gly Pro Gln Tyr Arg Leu Glu Lys Gln
                245                 250                 255

Ser Glu Pro Asn Val Ala Val Asp Leu Asp Ser Thr Leu Glu Ser Gln
            260                 265                 270

Ser Ala Trp Glu Phe Cys Leu Val Arg Glu Asn Ser Ser Arg Ala Asp
        275                 280                 285

Gly Val Phe Glu Glu Asp Ser Gln Ile Asp Ile Ala Thr Val Gln Asp
    290                 295                 300

Met Leu Ser Ser His His Tyr Lys Ser Phe Lys Val Ser Met Ile His
305                 310                 315                 320

Arg Leu Arg Phe Thr Thr Asp Val Gln Leu Gly Ile Ser Gly Asp Lys
                325                 330                 335

Val Glu Ile Asp Pro Val Thr Asn Gln Lys Ala Ser Thr Lys Phe Trp
            340                 345                 350

Ile Lys Gln Lys Pro Ile Ser Ile Asp Ser Asp Leu Leu Cys Ala Cys
        355                 360                 365

Asp Leu Ala Glu Glu Lys Ser Pro Ser His Ala Ile Phe Lys Leu Thr
    370                 375                 380

Tyr Leu Ser Asn His Asp Tyr Lys His Leu Tyr Phe Glu Ser Asp Ala
385                 390                 395                 400

Ala Thr Val Asn Glu Ile Val Leu Lys Val Asn Tyr Ile Leu Glu Ser
                405                 410                 415

Arg Ala Ser Thr Ala Arg Ala Asp Tyr Phe Ala Gln Lys Lys Ser Gly
            420                 425                 430

Arg
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 3987 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..1498

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GGCGGCCGCG GCAGGGCGGG CGCCGCGCGG AGGCAGGGCG GGCGTATTCA ATGGAAGTGT
GTTACCAGCT GCCGGTACTG CCCCTGGACA GGCCGGTCCC CCAGCACGTC CTCAGCCGCC
GAGGAGCCAT CAGCTTCAGC TCCAGCTCCG CTCTCTTCGG CTGCCCCAAT CCCCGGCAGC
TCTCTCAGAG GCGTGGAGCT ATTTCCTATG ACAGTTCTGA TCAGACTGCA TTATACATTC
GTATGCTAGG AGATGTACGT GTAAGGAGCC GAGCAGGATT TGAATCAGAA AGAAGAGGTT
CTCACCCATA TATTGATTTT CGTATTTTCC ACTCTCAATC TGAAATTGAA GTGTCTGTCT
CTGCAAGGAA TATCAGAAGG CTACTAAGTT TCCAGCGATA TCTTAGATCT TCACGCTTTT
TTCGTGGTAC TGCGGTTTCA AATTCCCTAA ACATTTTAGA TGATGATTAT AATGGACAAG
CCAAGTGTAT GCTGGAAAAA GTTGGAAATT GGAATTTTGA TATCTTTCTA TTTGATAGAC
TAACAAATGG AAATAGTCTA GTAAGCTTAA CCTTTCATTT ATTTAGTCTT CATGGATTAA
TTGAGTACTT CCATTTAGAT ATGATGAAAC TTCGTAGATT TTTAGTTATG ATTCAAGAAG
ATTACCACAG TCAAAATCCT TACCATAACG CAGTCCACGC TGCGGATGTT ACTCAGGCCA
TGCACTGTTA CTTAAAGGAA CCTAAGCTTG CCAATTCTGT AACTCCTTGG GATATCTTGC
TGAGCTTAAT TGCAGCTGCC ACTCATGATC TGGATCATCC AGGTGTTAAT CAACCTTTCC
TTATTAAAAC TAACCATTAC TTGGCAACTT TATACAAGAA TACCTCAGTA CTGGAAAATC
ACCACTGGAG ATCTGCAGTG GGCTTATTGA GAGAATCAGG CTTATTCTCA CATCTGCCAT
TAGAAAGCAG GCAACAAATG GAGACACAGA TAGGTGCTCT GATACTAGCC ACAGACATCA
GTCGCCAGAA TGAGTATCTG TCTTTGTTTA GGTCCCATTT GGATAGAGGT GATTTATGCC
TAGAAGACAC CAGACACAGA CATTTGGTTT TACAGATGGC TTTGAAATGT GCTGATATTT
GTAACCCATG TCGGACGTGG GAATTAAGCA AGCAGTGGAG TGAAAAAGTA ACGGAGGAAT
TCTTCCATCA AGGAGATATA GAAAAAAAAT ATCATTTGGG TGTGAGTCCA CTTTGCGATC

GTCACACTGA ATCTATTGCC AACATCCAGA TTGGTTTTAT GACTTACCTA GTGGAGCCTT
TATTTACAGA ATGGGCCAGG TTTTCCAATA CAAGGCTATC CCAGACAATG CTTGGACACG
TGGGGCTGAA TAAAGCCAGC TGGAAGGGAC TGCAGAGAGA ACAGTCGAGC AGTGAGGACA
CTGATGCTGC ATTTGAGTTG AACTCACAGT TATTACCTCA GGAAAATCGG TTATCATAAC
CCCCAGAACC AGTGGGACAA ACTGCCTCCT GGAGGTTTTT AGAAATGTGA AATGGGGTCT
TGAGGTGAGA GAACTTAACT CTTGACTGCC AAGGTTTCCA AGTGAGTGAT GCCAGCCAGC
ATTATTTATT TCCAAGATTT CCTCTGTTGG ATCATTTGAA CCCACTTGTT AATTGCAAGA
CCCGAACATA CAGCAATATG AATTTGGCTT TCATGTGAAA CCTTGAATAT NNAAAGCCCA
GCAGGAGAGA ATCCGAAAGG AGTAACAAAG GAAGTTTTGA TATGTGCCAC GACTTTTTCA
AAGCATCTAA TCTTCAAAAC GTCAAACTTG AATTGTTCAG CAACAATCTC TTGGAATTTA
ACCAGTCTGA TGCAACAATG TGTATCTTGT ACCTTCCACT AAGTTCTCTC TGAGAAAATG
GAAATGTGAA GTGCCCAGCC TCTGCNTGCC TCTGGCAAGA CAATGTTTAC AAATCAACTC
TGAAAATATT GGTTCTAAAT TGCCTTGGAG CATGATTGTG AAGGAACCAC TCAAACAAAT
TTAAAGATCA AACTTTAGAC TGCAGCTCTT TCCCCCTGGT TTGCCTTTTT CTTCTTTGGA
TGCCACCAAA GCCTCCCATT TGCTATAGTT TTATTTCATG CACTGGAAAC TGAGCATTTA
TCGTAGAGTA CCGCCAAGCT TTCACTCCAG TGCCGTTTGG CAATGCAATT TTTTTAGCA
ATTAGTTTTT AATTTGGGGT GGGAGGGGAA GAACACCAAT GTCCTAGCTG TATTATGATT
CTGCACTCAA GACATTGCAT GTTGTTTTCA CTACTGTACA CTTGACCTGC ACATGCGAGA
AAAAGGTGGA ATGTTTAAAA CACCATAATC AGCTCAGNGT ATTTGCCAAT CTGAAATAAA
AGTGGGATGG GAGAGCGTGT CCTTCAGATC AAGGGTACTA AAGTCCCTTT CGCTGCAGTG
AGTGAGAGGT ATGTTGTGTG TGAATGTACG GATGTGTGTT TGNGTGNATG TTTGTGCATG
TGTGACNGTG CATGTTATGT TTCTCCATGT GGGCAAAGAT TTGAAANGTA AGCTTTTATT
TATTATTTTA GAATGTGACA TAATGAGCAG CCACACTCGG GGGAGGGGAA GGTTGGTAGG
TAAGCTGTAA CAGATTGCTC CAGTTGCCTT AAACTATGCA CATAGCTAAG TGACCAAACT
TCTTGTTTTG ATTTGAAAAA AGTGCATTGT TTTCTTGTCC CTCCCTTTGA TGAAACGTTA
CCCTTTGACG GGCCTTTTGA TGTGAACAGA TGTTTTCTAG GACAAACTAT AAGGACTAAT

TTTAAACTTC AAACATTCCA CTTTTGTAAT TTGTTTTAAA TTGTTTTATG TATAGTAAGC
ACAACTGTAA TCTAGTTTTA AGAGAAACCG GTGCTTTCTT TTAGTTCATT TGTATTTCCC
TTGTTACTGT AAAAGACTGT TTATTAATTG TTTACAGTTT GTTGCAACAG CCATTTTCTT
GGGAGAAAGC TTGAGTGTAA AGCCATTTGT AAAAGGCTTT GCCATACTCA TTTTAATATG
TGCCTGTTGC TGTTAACTTT TGATGAATAA AAACCTATCT TTTCATGAAA CTTCTCTCTA
TACAAATTGA AATACATAAT GCTTTCTGGT TCTTCTTCAA ACCAAAACTT GTCAAATTCA
TAGACAAGAT AACAGTAAAA CTGATGAAAG TGTTCCATTG TTGGTATACC AGGAACAAGG
TTATAGAGAT GAAACTTCAA AGCTTCACTC TTCAGTAAGC TATAAGCCAT CTCTGTAAGA
TTGATTCCAA CTATTGCATA AGAATACCCT AATTTTGGAT GATTTGAACG GGAAAGAATC
TGATGAGCTT CACTAGTGTA ATTTTCACTG AAATACACAA GATTGATTAA CCCAAGTATG
CCCATGCCTC TGAAGTCTGT CTTGGGATCA TCACCCTGAA AACCAATTTC AGCCCACTGC
TTGGAGATTC TAGCGTTTAA CTTCTTCGTG GGCATTAGAA GATTCCAAAG CTTCATGAGT
AGCTCTTCAT GCTGTAGGTT ATCAGAATCA TATGGCCTTT TCCTCACACT TTCTACATCC
AAATACAGCT GTTTATAACC AGTTATCTGC AGTAAGCACA TCTTCATGCA TATTTTAAAA
CTGGCATCCT TCTCAGGGTT AATATTCTTT TCCTTCATAA TATCATCTAC ATATTTGTCC
ACTTCACTCT GAACAACATG TGTCGCCTTC TGTAAAACCT TATTCTTGGA GTATGTCAAG
GAATTTTCTA TCCTGTGTGT CCTTTGTGCA CCTACATAGG TATCAAATAT TCGCTGCAAT
TCACACTTCC CAGTCATCTG TCGTAATAGC CATTTCATCC AAAATCGAAA AAAGTGCCCA
TAGAAGAACT CCCACAAAGA AATAAACATT TTTTTTTCCT CACAGGAGCG GAAGAACTAG
GGGGAGCAGG AGCTGCAATG CGGCCGC

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3131 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

```
CTG CAG GAG GAC AAC TGC GAC ATC TTC CAG AAC CTC AGC AAG CGC CAG
Leu Gln Glu Asp Asn Cys Asp Ile Phe Gln Asn Leu Ser Lys Arg Gln
            270                 275                 280

CGC AGA GCC TAC GCA AGA TGG TCA TCG ACA TGG TGC TGG CCA CGG ACA
Arg Arg Ala Tyr Ala Arg Trp Ser Ser Thr Trp Cys Trp Pro Arg Thr
        285                 290                 295

TGT CCA AGC ACA TGACCCTCCT GGCTGACCTG AAGACCATGG TGGAGACCAA
Cys Pro Ser Thr
    300

GAAAGTGACC AGCTCAGGGG TCCTCCTGCT AGATAACTAC TCCGACCGCA TCCAGGTCCT

CCGGAACATG GTGCACTGTG CCGACCTCAG CAACCCCACC AAGCCGCTGG AGCTGTACCG

CCAGTGGACA GACCGCATCA TGGCCGAGTT CTTCCAGCAG GGTGACCGAG AGCGCGAGCG

TGGCATGGAA ATCAGCCCCA TGTGTGACAA GCACACTGCC TCCGTGGAGA AGTCTCAGGT

GGGTTTTATT GACTACATTG TGCACCCATT GTGGGAGACC TGGGCGGACC TTGTCCACCC

AGATGCCCAG GAGATCTTGG ACACTTTGGA GGACAACCGG GACTGGTACT ACAGCGCCAT

CCGGCAGAGC CCATCTCCGC CACCCGAGGA GGAGTCAAGG GGGCCAGGCC ACCCACCCCT

GCCTGACAAG TTCCAGTTTG AGCTGACGCT GGAGGAGGAA GAGGAGGAAG AAATATCAAT

GGCCCAGATA CCGTGCACAG CCCAAGAGGC ATTGACTGAG CAGGGATTGT CAGGAGTCGA

GGAAGCTCTG GATGCAACCA TAGCCTGGGA GGCATCCCCG GCCCAGGAGT CGTTGGAAGT

TATGGCACAG GAAGCATCCC TGGAGGCCGA GCTGGAGGCA GTGTATTTGA CACAGCAGGC

ACAGTCCACA GGCAGTGCAC CTGTGGCTCC GGATGAGTTC TCGTCCCGGG AGGAATTCGT

GGTTGCTGTA AGCCACAGCA GCCCCTCTGC CCTGGCTCTT CAAAGCCCCC TTCTCCCTGC

TTGGAGGACC CTGTCTGTTT CAGAGCATGC CCCGGGCCTC CCGGGCCTCC CCTCCACGGC

GGCCGAGGTG GAGGCCCAAC GAGAGCACCA GGCTGCCAAG AGGGCTTGCA GTGCCTGCGC

AGGGACATTT GGGGAGGACA CATCCGCACT CCCAGCTCCT GGTGGCGGGG GGTCAGGTGG

AGACCCTACC TGATCCCCAG ACCTCTGTCC CTGTTCCCCT CCACTCCTCC CCTCACTCCC

CTGCTCCCCC GACCACCTCC TCCTCTGCCT CAAAGACTCT TGTCCTCTTG TCCCTCCTGA

GATTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTACAACA CAAATGAATG GGCCATTTTA

TTGATTTTTA CCTCCTAATA GTGGATACAG GTTGCTGTGG TTTCCAGCAG GATCTCAGAT
```

GCAAAGGGAA GTGAAGAAAA CAGATGAATC CCTAGGGTAC CCCGCCATGG AACCAAACAC

CACGTCAACT GGAACTCTTC TTGCAAACGA AGGCTGAAGA TCAAGAATGA CATTCTCACA

CCACAGCACA GCTTAAATAC TTCTTTGACA AAAATAATAA TAAATTATAT TTGACTCAGA

AAATAAATTC TGTTCAGCAG AGTGACAGGA GGTAAAAATC AAATGAATGG GCAATGCGGC

CGC

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 302 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Met Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser His Lys Phe Lys
  1               5                  10                  15

Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser
             20                  25                  30

Gly Asn Gln Val Ser Glu Tyr Ile Ser Thr Thr Phe Leu Asp Lys Gln
         35                  40                  45

Asn Glu Val Glu Ile Pro Ser Pro Thr Met Lys Glu Arg Glu Lys Gln
     50                  55                  60

Gln Ala Pro Arg Pro Arg Pro Ser Gln Pro Pro Pro Pro Pro Val Pro
 65                  70                  75                  80

His Leu Gln Pro Met Ser Gln Ile Thr Gly Leu Lys Lys Leu Met His
                 85                  90                  95

Ser Asn Ser Leu Asn Asn Ser Asn Ile Pro Arg Phe Gly Val Lys Thr
            100                 105                 110

Asp Gln Glu Glu Leu Leu Ala Gln Glu Leu Glu Asn Leu Asn Lys Trp
        115                 120                 125

Gly Leu Asn Ile Phe Cys Val Ser Asp Tyr Ala Gly Gly Arg Ser Leu
    130                 135                 140

Thr Cys Ile Met Tyr Met Ile Phe Gln Glu Arg Asp Leu Leu Lys Lys
145                 150                 155                 160
```

```
Phe Arg Ile Pro Val Asp Thr Met Val Thr Tyr Met Leu Thr Leu Glu
                165                 170                 175

Asp His Tyr His Ala Asp Val Ala Tyr His Asn Ser Leu His Ala Ala
            180                 185                 190

Asp Val Leu Gln Ser Thr His Val Leu Leu Ala Thr Pro Ala Leu Asp
        195                 200                 205

Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Leu Phe Ala Ala Ala
    210                 215                 220

Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn
225                 230                 235                 240

Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu
                245                 250                 255

Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Asp Asn Cys
            260                 265                 270

Asp Ile Phe Gln Asn Leu Ser Lys Arg Gln Arg Arg Ala Tyr Ala Arg
        275                 280                 285

Trp Ser Ser Thr Trp Cys Trp Pro Arg Thr Cys Pro Ser Thr
    290                 295                 300
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3186 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 139..2348

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
GCGGCCGCGG CGGTGCAGCA GAGGCGCCTC GGGCAGGAGG AGGGCGGCTT CTGCGAGGGC

AGCCTGAGGT ATTAAAAAGT GTCAGCAAAC TGCATTGAAT AACAGACATC CTAAGAGGGG

ATATTTTCCA CCTCTATA ATG AAG AAA AGC AGG AGT GTG ATG ACG GTG ATG
```

```
                    Met Lys Lys Ser Arg Ser Val Met Thr Val Met
                     1               5                   10

GCT GAT GAT AAT GTT AAA GAT TAT TTT GAA TGT AGC TTG AGT AAA TCC
Ala Asp Asp Asn Val Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser
             15                  20                  25

TAC AGT TCT TCC AGT AAC ACA CTT GGG ATC GAC CTC TGG AGA GGG AGA
Tyr Ser Ser Ser Ser Asn Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg
         30                  35                  40

AGG TGT TGC TCA GGA AAC TTA CAG TTA CCA CCA CTG TCT CAA AGA CAG
Arg Cys Cys Ser Gly Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln
     45                  50                  55

AGT GAA AGG GCA AGG ACT CCT GAG GGA GAT GGT ATT TCC AGG CCG ACC
Ser Glu Arg Ala Arg Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr
 60                  65                  70                  75

ACA CTG CCT TTG ACA ACG CTT CCA AGC ATT GCT ATT ACA ACT GTA AGC
Thr Leu Pro Leu Thr Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser
                 80                  85                  90

CAG GAG TGC TTT GAT GTG GAA AAT GGC CCT TCC CCA GGT CGG AGT CCA
Gln Glu Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro
             95                 100                 105

CTG GAT CCC CAG GCC AGC TCT TCC GCT GGG CTG GTA CTT CAC GCC ACC
Leu Asp Pro Gln Ala Ser Ser Ser Ala Gly Leu Val Leu His Ala Thr
        110                 115                 120

TTT CCT GGG CAC AGC CAG CGC AGA GAG TCA TTT CTC TAC AGA TCA GAC
Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp
    125                 130                 135

AGC GAC TAT GAC TTG TCA CCA AAG GCG ATG TCG AGA AAC TCT TCT CTT
Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu
140                 145                 150                 155

CCA AGC GAG CAA CAC GGC GAT GAC TTG ATT GTA ACT CCT TTT GCC CAG
Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln
                160                 165                 170

GTC CTT GCC AGC TTG CGA AGT GTG AGA AAC AAC TTC ACT ATA CTG ACA
Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Ile Leu Thr
            175                 180                 185

AAC CTT CAT GGT ACA TCT AAC AAG AGG TCC CCA GCT GCT AGT CAG CCT
Asn Leu His Gly Thr Ser Asn Lys Arg Ser Pro Ala Ala Ser Gln Pro
        190                 195                 200

CCT GTC TCC AGA GTC AAC CCA CAA GAA GAA TCT TAT CAA AAA TTA GCA
```

```
Pro Val Ser Arg Val Asn Pro Gln Glu Glu Ser Tyr Gln Lys Leu Ala
    205                 210                 215

ATG GAA ACG CTG GAG GAA TTA GAC TGG TGT TTA GAC CAG CTA GAG ACC
Met Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr
220                 225                 230                 235

ATA CAG ACC TAC CGG TCT GTC AGT GAG ATG GCT TCT AAC AAG TTC AAA
Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys
                240                 245                 250

AGA ATG CTG AAC CGG GAG CTG ACA CAC CTC TCA GAG ATG AGC CGA TCA
Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser
            255                 260                 265

GGG AAC CAG GTG TCT GAA TAC ATT TCA AAT ACT TTC TTA GAC AAG CAG
Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln
        270                 275                 280

AAT GAT GTG GAG ATC CCA TCT CCT ACC CAG AAA GAC AGG GAG AAA AAG
Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys
    285                 290                 295

AAA AAG CAG CAG CTC ATG ACC CAG ATA AGT GGA GTG AAG AAA TTA ATG
Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met
300                 305                 310                 315

CAT AGT TCA AGC CTA AAC AAT ACA AGC ATC TCA CGC TTT GGA GTC AAC
His Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn
                320                 325                 330

ACT GAA AAT GAA GAT CAC CTG GCC AAG GAG CTG GAA GAC CTG AAC AAA
Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys
            335                 340                 345

TGG GGT CTT AAC ATC TTT AAT GTG GCT GGA TAT TCT CAC AAT AGA CCC
Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro
        350                 355                 360

CTA ACA TGC ATC ATG TAT GCT ATA TTC CAG GAA AGA GAC CTC CTA AAG
Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys
    365                 370                 375

ACA TTC AGA ATC TCA TCT GAC ACA TTT ATA ACC TAC ATG ATG ACT TTA
Thr Phe Arg Ile Ser Ser Asp Thr Phe Ile Thr Tyr Met Met Thr Leu
380                 385                 390                 395

GAA GAC CAT TAC CAT TCT GAC GTG GCA TAT CAC AAC AGC CTG CAC GCT
Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala
                400                 405                 410

GCT GAT GTA GCC CAG TCG ACC CAT GTT CTC CTT TCT ACA CCA GCA TTA
```

Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu
415 420 425

GAC GCT GTC TTC ACA GAT TTG GAG ATC CTG GCT GCC ATT TTT GCA GCT
Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala
430 435 440

GCC ATC CAT GAC GTT GAT CAT CCT GGA GTC TCC AAT CAG TTT CTC ATC
Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile
445 450 455

AAC ACA AAT TCA GAA CTT GCT TTG ATG TAT AAT GAT GAA TCT GTG TTG
Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu
460 465 470 475

GAA AAT CAT CAC CTT GCT GTG GGT TTC AAA CTG CTG CAA GAA GAA CAC
Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His
480 485 490

TGT GAC ATC TTC ATG AAT CTC ACC AAG AAG CAG CGT CAG ACA CTC AGG
Cys Asp Ile Phe Met Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg
495 500 505

AAG ATG GTT ATT GAC ATG GTG TTA GCA ACT GAT ATG TCT AAA CAT ATG
Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met
510 515 520

AGC CTG CTG GCA GAC CTG AAG ACA ATG GTA GAA ACG AAG AAA GTT ACA
Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr
525 530 535

AGT TCA GGC GTT CTT CTC CTA GAC AAC TAT ACC GAT CGC ATT CAG GTC
Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val
540 545 550 555

CTT CGC AAC ATG GTA CAC TGT GCA GAC CTG AGC AAC CCC ACC AAG TCC
Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser
560 565 570

TTG GAA TTG TAT CGG CAA TGG ACA GAC CGC ATC ATG GAG GAA TTT TTC
Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe
575 580 585

CAG CAG GGA GAC AAA GAG CGG GAG AGG GGA ATG GAA ATT AGC CCA ATG
Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met
590 595 600

TGT GAT AAA CAC ACA GCT TCT GTG GAA AAA TCC CAG GTT GGT TTC ATC
Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile
605 610 615

GAC TAC ATT GTC CAT CCA TTG TGG GAG ACA TGG GCA GAT TTG GTA CAG

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Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln
620                 625                 630                 635

CCT GAT GCT CAG GAC ATT CTC GAT ACC TTA GAA GAT AAC AGG AAC TGG
Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp
                640                 645                 650

TAT CAG AGC ATG ATA CCT CAA AGT CCC TCA CCA CCA CTG GAC GAG CAG
Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Gln
            655                 660                 665

AAC AGG GAC TGC CAG GGT CTG ATG GAG AAG TTT CAG TTT GAA CTG ACT
Asn Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr
        670                 675                 680

CTC GAT GAG GAA GAT TCT GAA GGA CCT GAG AAG GAG GGA GAG GGA CAC
Leu Asp Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His
    685                 690                 695

AGC TAT TTC AGC AGC ACA AAG ACG CTT TGT GTG ATT GAT CCA GAA AAC
Ser Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn
700                 705                 710                 715

AGA GAT TCC CTG GGA GAG ACT GAC ATA GAC ATT GCA ACA GAA GAC AAG
Arg Asp Ser Leu Gly Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys
                720                 725                 730

TCC CCC GTG GAT ACA TA ATCCCCCTCT CCCTGTGGAG ATGAACATTC
Ser Pro Val Asp Thr
            735

TATCCTTGAT GAGCATGCCA GCTATGTGGT AGGGCCAGCC CACCATGGGG GCCAAGACCT

GCACAGGACA AGGGCCACCT GGCCTTTCAG TTACTTGAGT TTGGAGTCAG AAAGCAAGAC

CAGGAAGCAA ATAGCAGCTC AGGAAATCCC ACGGTTGACT TGCCTTGATG GCAAGCTTGG

TGGAGAGGGC TGAAGCTGTT GCTGGGGGCC GATTCTGATC AAGACACATG GCTTGAAAAT

GGAAGACACA AAACTGAGAG ATCATTCTGC ACTAAGTTTC GGGAACTTAT CCCCGACAGT

GACTGAACTC ACTGACTAAT AACTTCATTT ATGAATCTTC TCACTTGTCC CTTTGTCTGC

CAACCTGTGT GCCTTTTTTG TAAAACATTT TCATGTCTTT AAAATGCCTG TTGAATACCT

GGAGTTTAGT ATCAACTTCT ACACAGATAA GCTTTCAAAG TTGACAAACT TTTTTGACTC

TTTCTGGAAA AGGGAAAGAA AATAGTCTTC CTTCTTTCTT GGGCAATATC CTTCACTTTA

CTACAGTTAC TTTTGCAAAC AGACAGAAAG GATACACTTC TAACCACATT TTACTTCCTT

CCCCTGTTGT CCAGTCCAAC TCCACAGTCA CTCTTAAAAC TTCTCTCTGT TTGCCTGCCT
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CCAACAGTAC TTTTAACTTT TTGCTGTAAA CAGAATAAAA TTGAACAAAT TAGGGGGTAG

AAAGGAGCAG TGGTGTCGTT CACCGTGAGA GTCTGCATAG AACTCAGCAG TGTGCCCTGC

TGTGTCTTGG ACCCTGCAAT GCGGCCGC
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 736 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
Met Lys Lys Ser Arg Ser Val Met Thr Val Met Ala Asp Asp Asn Val
  1               5                  10                  15

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
             20                  25                  30

Asn Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
         35                  40                  45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
     50                  55                  60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr
 65                  70                  75                  80

Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp
                 85                  90                  95

Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala
            100                 105                 110

Ser Ser Ser Ala Gly Leu Val Leu His Ala Thr Phe Pro Gly His Ser
        115                 120                 125

Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu
    130                 135                 140

Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His
145                 150                 155                 160

Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu
                165                 170                 175
```

Arg Ser Val Arg Asn Asn Phe Thr Ile Leu Thr Asn Leu His Gly Thr
180 185 190

Ser Asn Lys Arg Ser Pro Ala Ala Ser Gln Pro Pro Val Ser Arg Val
195 200 205

Asn Pro Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu
210 215 220

Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg
225 230 235 240

Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg
245 250 255

Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser
260 265 270

Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile
275 280 285

Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln Gln Leu
290 295 300

Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
305 310 315 320

Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp
325 330 335

His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile
340 345 350

Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met
355 360 365

Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Arg Ile Ser
370 375 380

Ser Asp Thr Phe Ile Thr Tyr Met Met Thr Leu Glu Asp His Tyr His
385 390 395 400

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
405 410 415

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
420 425 430

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
435 440 445

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu

450 455 460

Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
465 470 475 480

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Met
485 490 495

Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
500 505 510

Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
515 520 525

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
530 535 540

Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
545 550 555 560

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
565 570 575

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
580 585 590

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
595 600 605

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
610 615 620

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
625 630 635 640

Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
645 650 655

Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Gln Asn Arg Asp Cys Gln
660 665 670

Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Asp Glu Glu Asp
675 680 685

Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His Ser Tyr Phe Ser Ser
690 695 700

Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Gly
705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Pro Val Asp Thr
725 730 735

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1276 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..504

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GCGGCCGCAT TGCGTGGTGG CGGCGGCCGA GCCTCGCTTT GAGAGACAGA ATGGACAGCA

AATTATGGAT GAACCTATGG GAGAGGAGGA GATTAACCCA CAAACTGAAG AAGTCAGTAT

CAAAGAAATT GCAATCACAC ATCATGTAAA GGAAGGACAT GAAAAGGCAG ATCCTTCCCA

GTTTGAACTT TTAAAAGTAT TAGGGCAGGG ATCATTTGGA AAGGTTTTCT TAGTTAAAAA

AATCTCAGGC TCTGATGCTA GGCAGCTTTA TGCCATGAAG GTATTGAAGA AGGCCACACT

GAAAGTTCGA GACCGAGTTC GGACAAAAAT GGAACGTGAT ATCTTGGTAG AGGTTAATCA

TCCTTTTATT GTCAAGTTGC ATTATCTTTT CAAACTGAAG GGAAGTTGTA TCTTATTTGG

ATTTTCTCAG GGGAGGAGAT TTGTTTACAC GCTTATCCAA AGAGGTGATG TTCACAGAAG

AAGATGTCAA ATTCTACCTG GCTGAACTTG CACTTGCTTT AGACCATCTA CNTAGCCTGG

GAATAATTTA TAGAGACTTA AAACCAGAAA ATATCTTCTT GATGAAGAAG GTCACATCAA

GTTAACAGAT TTCGGCCTAA GTAAAGAGTC TATTGACCAT GAAAAGAAGG CATATCTTTT

TGTGGAACTG TGGAGTATAT GGCTCCAGAA GTAGTTAATC GTCGAGGTCA TACTCAGAGT

GCTGACTGGT GGTCTTTTGG TGTGTTAATG TTTGAAATGC TTACTGGTAC CACTCCCTTT

CCAAGGAAAA GATCGAAAAG AAACAATGAC TATGATTCTT AAAGCCAAAA CTTGGAATGC

CACAGTTTTT GAGTCCTGAA GCGCAGAGTC TTTTACGAAT GCTTTTMAAG CGAAATCCTG

CAAACAGATT AGGTGCAGGA CCAGATGGAG TTGAAGAAAT TAAAAGACAT TCATTTTTCT

CAACGATAGA CTGGAATAAA CTGTATAGAG AGAAATTCAT CCGCCATTTA AACCTGCAAC

GGGCAGGCCT GAAGATACAT TCTATTTTGA TCCTGAGTTT ACTGCAAAAA CTCCCAAAGA

TTCACCTGGC ATTCCACCTA GTGCTAATGC ACATCAGCTT TTTCGGGGGT TTAGTTTTGT

TGCTATTACC TCAGATGATG AAAGCCAAGC TATGCAGACA GTTGGTGTAC ATTCAATTGT

TCAGCAGTTA CACAGGAACA GTATNCAGTT TACTGATGGA TATGAAGTAA AAGAAGATAT

TGGAGTTGGC TCCTAC

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2384 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1541

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1859..2383

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
GCG GCC GCA TTC GGG GAC AGC GGC GGG CGG CTG GGA CGG CGG GTG CGG
Ala Ala Ala Phe Gly Asp Ser Gly Gly Arg Leu Gly Arg Arg Val Arg
  1               5                  10                  15

CGG GGC CGA GCC CGC ACG ATG CCT CAC TTC ACC GTG GTG CCA GTG GAC
Arg Gly Arg Ala Arg Thr Met Pro His Phe Thr Val Val Pro Val Asp
             20                  25                  30

GGG CCG AGG CGC GGC GAC TAT GAC AAC CTC GAG GGG CTC AGT TGG GTG
Gly Pro Arg Arg Gly Asp Tyr Asp Asn Leu Glu Gly Leu Ser Trp Val
         35                  40                  45

GAC TAC GGG GAG CGC GCC GAG CTG GAT GAC TCG GAC GGA CAT GGC AAC
Asp Tyr Gly Glu Arg Ala Glu Leu Asp Asp Ser Asp Gly His Gly Asn
     50                  55                  60

CAC AGA GAG AGC AGC CCT TTT CTT TCC CCC TTG GAG GCT TCC AGA GGA
```

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His Arg Glu Ser Ser Pro Phe Leu Ser Pro Leu Glu Ala Ser Arg Gly
 65                  70                  75                  80

ATT GAC TAC TAT GAC AGG AAC CTG GCA CTG TTT GAG GAA GAG CTG GAC
Ile Asp Tyr Tyr Asp Arg Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp
                 85                  90                  95

ATC CGC CCA AAG GTA TCG TCT CTT CTG GGA AAG CTC GTC AGC TAC ACC
Ile Arg Pro Lys Val Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr
            100                 105                 110

AAC CTC ACC CAG GGC GCC AAA GAG CAT GAG GAG GCC GAG AGT GGG GAG
Asn Leu Thr Gln Gly Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu
        115                 120                 125

GGC ACC CGC CGG AGG GCA GCC GAG GCA CCC AGC ATG GGC ACC CTC ATG
Gly Thr Arg Arg Arg Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met
    130                 135                 140

GGG GTG TAC CTG CCC TGC CTG CAG AAT ATC TTT GGG GTT ATC CTC TTC
Gly Val Tyr Leu Pro Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe
145                 150                 155                 160

CTG CGG CTG ACC TGG ATG GTG GGC ACA GCA GGT GTG CTA CAG GCC CTC
Leu Arg Leu Thr Trp Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu
                165                 170                 175

CTC ATC GTG CTT ATC TGC TGC TGT TGT ACC CTG CTG ACG GCC ATC TCC
Leu Ile Val Leu Ile Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser
            180                 185                 190

ATG AGT GCC ATC GCC ACC AAC GGT GTG GTT CCA GCT GGG GGC TCC TAT
Met Ser Ala Ile Ala Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr
        195                 200                 205

TTC ATG ATC TCT CGT TCA CTG GGG CCA GAA TTT GGA GGT GCT GTG GGC
Phe Met Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly
    210                 215                 220

CTG TGC TTC TAC CTG GGA ACA ACA TTC GCA GCA GCC ATG TAC ATC CTG
Leu Cys Phe Tyr Leu Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu
225                 230                 235                 240

GGG GCC ATC GAG ATC TTG CTG ACC TAC ATT GCC CCA CCA GCT GCC ATT
Gly Ala Ile Glu Ile Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile
                245                 250                 255

TTT TAC CCA TCG GGT GCT CAT GAC ACG TCG AAT GCC ACT TTG AAC AAT
Phe Tyr Pro Ser Gly Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn
            260                 265                 270

ATG CGT GTG TAT GGG ACC ATT TTC CTG GCC TTC ATG ACC CTG GTG GTG
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Met Arg Val Tyr Gly Thr Ile Phe Leu Ala Phe Met Thr Leu Val Val
        275                 280                 285

TTT GTG GGG GTC AAG TAT GTG AAC AAA TTT GCC TCG CTC TTC CTG GCC
Phe Val Gly Val Lys Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala
    290                 295                 300

TGT GTG ATC ATC TCC ATC CTC TCC ATC TAT GCT GGG GGC ATA AAG TCT
Cys Val Ile Ile Ser Ile Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser
305                 310                 315                 320

ATA TTT GAC CCT CCC GTG TTT CCG GTA TGC ATG CTG GGC AAC AGG ACC
Ile Phe Asp Pro Pro Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr
                325                 330                 335

CTG TCC CGG GAC CAG TTT GAC ATC TGT GCC AAG ACA GCT GTA GTG GAC
Leu Ser Arg Asp Gln Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp
            340                 345                 350

AAT GAG ACA GTG GCC ACC CAG CTA TGG AGT TTC TTC TGC CAC AGC CCC
Asn Glu Thr Val Ala Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro
        355                 360                 365

AAC CTT ACG ACC GAC TCC TGT GAC CCC TAC TTC ATG CTC AAC AAT GTG
Asn Leu Thr Thr Asp Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val
    370                 375                 380

ACC GAG ATC CCT GGC ATC CCC GGG GCA GCT GCT GGT GTG CTC CAG GAA
Thr Glu Ile Pro Gly Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu
385                 390                 395                 400

AAC CTG TGG AGC GCC TAC CTG GAG AAG GGT GAC ATC GTG GAG AAG CAT
Asn Leu Trp Ser Ala Tyr Leu Glu Lys Gly Asp Ile Val Glu Lys His
                405                 410                 415

GGG CTG CCC TCC GCA GAT GCC CCG AGC CTG AAG GAG AGC CTG CCT CTG
Gly Leu Pro Ser Ala Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu
            420                 425                 430

TAC GTG GTC GCT GAC ATC GCC ACA TCC TTC ACC GTG CTG GTC GGC ATC
Tyr Val Val Ala Asp Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile
        435                 440                 445

TTC TTC CCT TCT GTA ACA GGT ATG GCG ATG GTG TCA GCA GGA ACT TGG
Phe Phe Pro Ser Val Thr Gly Met Ala Met Val Ser Ala Gly Thr Trp
    450                 455                 460

TGG TGG GCA CAC TGG CCT GGC CTT CAC CCT GGG TCA TCG TCA TCG GCT
Trp Trp Ala His Trp Pro Gly Leu His Pro Gly Ser Ser Ser Ser Ala
465                 470                 475                 480

CCT TCT TTT CAA CGT GTG GCG CTG GCC TCC AGA GCC TCA CAG GGG CAC
```

Pro Ser Phe Gln Arg Val Ala Leu Ala Ser Arg Ala Ser Gln Gly His
485 490 495

CAC GCC TAT TGC AGG CCA TTG CCA AGG ACA ACA TCA TCC CCT TCC TCC
His Ala Tyr Cys Arg Pro Leu Pro Arg Thr Thr Ser Ser Pro Ser Ser
500 505 510

GGG TG AGCCCCTCTG CACTCCCCCA TGGCCTGGCT GCTCCCAGGC CCTCGCCCGG
Gly

CTGGGGAGAG AGATAGGGAA CACAGATGCA GCACGTCCTG CCCTTATTGC CCCCGGGCCA

GGCGGCCATC CATGAGGAGC TACTGAGAAG TGCCCTGGGC CTGGCACTCA CCTGGGCCTG

GAGCTGCCTG GACCCAGAAT CTTCATGGCC TGTTTAGGGC TCATCCAAAG GAGAGAGGCC

TGGTGAGGTG GAATCAGGGA GACTGGTGAC ACCCATAGGG ATAGACACAG GGGCGGCCTG

AGCCCCCAAG GCGGGCCCTG GGGGTGA GGG AGG CCA GGC TGG GGT CTG GGG
Gly Arg Pro Gly Trp Gly Leu Gly
1 5

CCC AAG GTG TGG AAT GGG GGT GAC AGG ACC CAG CTT CCT TCC TGG TGC
Pro Lys Val Trp Asn Gly Gly Asp Arg Thr Gln Leu Pro Ser Trp Cys
10 15 20

ACA CAG GTG TTT GGC CAC GGG AAG GTG AAT GGT GAA CCC ACA TGG GCA
Thr Gln Val Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala
25 30 35 40

CTC CTC CTG ACG GCA CTC ATC GCC GAG CTG GGC ATC CTC ATC GCC TCC
Leu Leu Leu Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser
45 50 55

CTC GAC ATG GTG GCC CCC ATC TTA TCC ATG TTC TTT CTG ATG TGC TAC
Leu Asp Met Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr
60 65 70

CTG TTC GTG AAC CTC GCC TGT GCG GTG CAG ACA CTC CTG AGG ACC CCC
Leu Phe Val Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro
75 80 85

AAC TGG CGG CCC CGG TTC AAG TAC TAT CAC TGG GCG CTG TCC TTC CTG
Asn Trp Arg Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu
90 95 100

GGC ATG AGT CTC TGC CTG GCC CTT ATG TTT GTC TCC TCC TGG TAC TAT
Gly Met Ser Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr
105 110 115 120

GCC CTG GTG GCC ATG CTC ATC GCC GGC ATG ATC TAC AAA TAC ATC GAG

Ala Leu Val Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu
125 130 135

TAC CAA GGG GCT GAG AAG GAG TGG GGT GAC GGG ATC CGA GGC CTG TCC
Tyr Gln Gly Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser
140 145 150

CTG AGC GCT GCC CGC TAC GCG CTG TTG CGG CTG GAG GAG GGG CCT CCT
Leu Ser Ala Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro
155 160 165

CAC ACC AAG AAC TGG CGG CCG C
His Thr Lys Asn Trp Arg Pro
170 175

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Ala Ala Ala Phe Gly Asp Ser Gly Gly Arg Leu Gly Arg Arg Val Arg
1 5 10 15

Arg Gly Arg Ala Arg Thr Met Pro His Phe Thr Val Val Pro Val Asp
20 25 30

Gly Pro Arg Arg Gly Asp Tyr Asp Asn Leu Glu Gly Leu Ser Trp Val
35 40 45

Asp Tyr Gly Glu Arg Ala Glu Leu Asp Asp Ser Asp Gly His Gly Asn
50 55 60

His Arg Glu Ser Ser Pro Phe Leu Ser Pro Leu Glu Ala Ser Arg Gly
65 70 75 80

Ile Asp Tyr Tyr Asp Arg Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp
85 90 95

Ile Arg Pro Lys Val Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr
100 105 110

Asn Leu Thr Gln Gly Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu
115 120 125

Gly Thr Arg Arg Arg Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met

130 135 140

Gly Val Tyr Leu Pro Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe
145 150 155 160

Leu Arg Leu Thr Trp Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu
165 170 175

Leu Ile Val Leu Ile Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser
180 185 190

Met Ser Ala Ile Ala Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr
195 200 205

Phe Met Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly
210 215 220

Leu Cys Phe Tyr Leu Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu
225 230 235 240

Gly Ala Ile Glu Ile Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile
245 250 255

Phe Tyr Pro Ser Gly Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn
260 265 270

Met Arg Val Tyr Gly Thr Ile Phe Leu Ala Phe Met Thr Leu Val Val
275 280 285

Phe Val Gly Val Lys Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala
290 295 300

Cys Val Ile Ile Ser Ile Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser
305 310 315 320

Ile Phe Asp Pro Pro Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr
325 330 335

Leu Ser Arg Asp Gln Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp
340 345 350

Asn Glu Thr Val Ala Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro
355 360 365

Asn Leu Thr Thr Asp Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val
370 375 380

Thr Glu Ile Pro Gly Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu
385 390 395 400

Asn Leu Trp Ser Ala Tyr Leu Glu Lys Gly Asp Ile Val Glu Lys His
405 410 415

Gly Leu Pro Ser Ala Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu
420 425 430

Tyr Val Val Ala Asp Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile
435 440 445

Phe Phe Pro Ser Val Thr Gly Met Ala Met Val Ser Ala Gly Thr Trp
450 455 460

Trp Trp Ala His Trp Pro Gly Leu His Pro Gly Ser Ser Ser Ser Ala
465 470 475 480

Pro Ser Phe Gln Arg Val Ala Leu Ala Ser Arg Ala Ser Gln Gly His
485 490 495

His Ala Tyr Cys Arg Pro Leu Pro Arg Thr Thr Ser Ser Pro Ser Ser
500 505 510

Gly

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Gly Arg Pro Gly Trp Gly Leu Gly Pro Lys Val Trp Asn Gly Gly Asp
1 5 10 15

Arg Thr Gln Leu Pro Ser Trp Cys Thr Gln Val Phe Gly His Gly Lys
20 25 30

Val Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu Thr Ala Leu Ile Ala
35 40 45

Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp Met Val Ala Pro Ile Leu
50 55 60

Ser Met Phe Phe Leu Met Cys Tyr Leu Phe Val Asn Leu Ala Cys Ala
65 70 75 80

Val Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg Pro Arg Phe Lys Tyr
85 90 95

Tyr His Trp Ala Leu Ser Phe Leu Gly Met Ser Leu Cys Leu Ala Leu
100 105 110

Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val Ala Met Leu Ile Ala
115 120 125

Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly Ala Glu Lys Glu Trp
130 135 140

Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala Ala Arg Tyr Ala Leu
145 150 155 160

Leu Arg Leu Glu Glu Gly Pro Pro His Thr Lys Asn Trp Arg Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1675 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 492..1330

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

AAGCTTGCGG CCGCATTGCG AGAACGAGAA CGGGAGCGAG AGAGAGAGCG AGAGAGGGAA

CGGGAGCGAG AAAGAGAAAA AGACAAAAAA CGGGACCGAG AAGAAGATGA AGAAGATGCA

TACGAACGAA GAAAACTTGA AAGAAAACTC CGAGAGAAAG AAGCTGCTTA TCAAGAGCGC

CTTAAGAATT GGGAAATCAG AGAACGAAAG AAAACCCGGG AATATGAGAA AGAAGCTGAA

AGAGAAGAAG AAAGAAGAAG AGAAATGGCC AAAGAAGCTA AACGACTAAA AGAATTCTTA

GAAGACTATG ATGATGATAG AGATGACCCC AAATATTACA GAGGAAGTGC TCTTCAGAAA

AGGTTGCGTG ATAGAGAAAA GGAAATGGAA GCAGATGAAC GAGATAGGAA GAGAGAGAAG

GAGGAGCTTG AGGAAATCAG GCAGCGCTTC TGGCAGAAGG GCATCCAGAT CCAGATGCAG

AGCTCCAGAG G ATG GAA CAA GAG GCT GAG AGG CGC AGG CAG CCA CAA ATA
Met Glu Gln Glu Ala Glu Arg Arg Arg Gln Pro Gln Ile
1 5 10

AAG CAA GAG CCA GAA TCA GAA GAG GAG GAA GAA GAA AAG CAA GAA AAA
Lys Gln Glu Pro Glu Ser Glu Glu Glu Glu Glu Glu Lys Gln Glu Lys
15 20 25

GAA GAA AAA CGA GAA GAA CCC ATG GAA GAG GAA GAG GAG CCA GAG CAA
Glu Glu Lys Arg Glu Glu Pro Met Glu Glu Glu Glu Glu Pro Glu Gln
30 35 40 45

AAG CCT TGT CTG AAA CCT ACT CTG AGG CCC ATC AGC TCT GCT CCA TCT
Lys Pro Cys Leu Lys Pro Thr Leu Arg Pro Ile Ser Ser Ala Pro Ser
50 55 60

GTT TCC TCT GCC AGT GGC AAT GCA ACA CCT AAC ACT CCT GGG GAT GAG
Val Ser Ser Ala Ser Gly Asn Ala Thr Pro Asn Thr Pro Gly Asp Glu
65 70 75

TCT CCC TGT GGT ATT ATT ATT CCT CAT GAA AAC TCA CCA GAT CAA CAG
Ser Pro Cys Gly Ile Ile Ile Pro His Glu Asn Ser Pro Asp Gln Gln
80 85 90

CAA CCT GAG GAG CAT AGG CCA AAA ATA GGA CTA AGT CTT AAA CTG GGT
Gln Pro Glu Glu His Arg Pro Lys Ile Gly Leu Ser Leu Lys Leu Gly
95 100 105

GCT TCC AAT AGT CCT GGT CAG CCT AAT TCT GTG AAG AGA AAG AAA CTA
Ala Ser Asn Ser Pro Gly Gln Pro Asn Ser Val Lys Arg Lys Lys Leu
110 115 120 125

CCT GTA GAT AGT GTC TTT AAC AAA TTT GAG GAT GAA GAC AGT GAT GAC
Pro Val Asp Ser Val Phe Asn Lys Phe Glu Asp Glu Asp Ser Asp Asp
130 135 140

GTA CCC CGA AAA AGG AAA CTG GTT CCC TTG GAT TAT GGT GAA GAT GAT
Val Pro Arg Lys Arg Lys Leu Val Pro Leu Asp Tyr Gly Glu Asp Asp
145 150 155

AAA AAT GCA ACC AAA GGC ACT GTA AAC ACT GAA GAA AAG CGT AAA CAC
Lys Asn Ala Thr Lys Gly Thr Val Asn Thr Glu Glu Lys Arg Lys His
160 165 170

ATT AAG AGT CTC ATT GAG AAA ATC CCT ACA GCC AAA CCT GAG CTC TTC
Ile Lys Ser Leu Ile Glu Lys Ile Pro Thr Ala Lys Pro Glu Leu Phe
175 180 185

GCT TAT CCC CTG GAT TGG TCT ATT GTG GAT TCT ATA CTG ATG GAA CGT
Ala Tyr Pro Leu Asp Trp Ser Ile Val Asp Ser Ile Leu Met Glu Arg
190 195 200 205

CGA ATT AGA CCA TGG ATT AAT AAG AAA ATC ATA GAA TAT ATA GGT GAA
Arg Ile Arg Pro Trp Ile Asn Lys Lys Ile Ile Glu Tyr Ile Gly Glu
210 215 220

GAA GAA GCT ACA TTA GTT GAT TTT GTT TGT TCT AAG GTT ATG GCT CAT
Glu Glu Ala Thr Leu Val Asp Phe Val Cys Ser Lys Val Met Ala His
225 230 235

AGT TCA CCC CAG AGC ATT TTA GAT GAT GTT GCC ATG GTA CTT GAT GAA
Ser Ser Pro Gln Ser Ile Leu Asp Asp Val Ala Met Val Leu Asp Glu
240 245 250

GAA GCA GAA GTT TTT ATA GTC AAA ATG TGG AGA TTA TTG ATA TAT GAA
Glu Ala Glu Val Phe Ile Val Lys Met Trp Arg Leu Leu Ile Tyr Glu
255 260 265

ACA GAA GCC AAG AAA ATT GGT CTT GTG AAG TA AAACTTTTTA TATTTAGAGT
Thr Glu Ala Lys Lys Ile Gly Leu Val Lys
270 275

TCCATTTCAG ATTTCTTCTT TGCCACCCTT TTAAGGACTT TGAATTTTTC TTTGTCTTTG

AAGACATTGT GAGATCTGTA ATTTTTTTTT TTTGTAGAAA ATGTGAATTT TTTGGTCCTC

TAATTTGTTG TTGCCCTGTG TACTCCCTTG GTTGTAAAGT CATCTGAATC CTTGGTTCTC

TTTATACTCA CCAGGTACAA ATTACTGGTA TGTTTTATAA GCCGCAGCTA CTGTACACAG

CCTATCTGAT ATAATCTTGT TCTGCTGATT TGTTTCTTGT AAATATTAAA ACGACTCCCC

AATTAAAAAA AAAAAATGCG GCCGC

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 279 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Glu Gln Glu Ala Glu Arg Arg Arg Gln Pro Gln Ile Lys Gln Glu
1 5 10 15

Pro Glu Ser Glu Glu Glu Glu Glu Glu Lys Gln Glu Lys Glu Glu Lys
20 25 30

Arg Glu Glu Pro Met Glu Glu Glu Glu Glu Pro Glu Gln Lys Pro Cys
35 40 45

Leu Lys Pro Thr Leu Arg Pro Ile Ser Ser Ala Pro Ser Val Ser Ser
50 55 60

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Ala Ser Gly Asn Ala Thr Pro Asn Thr Pro Gly Asp Glu Ser Pro Cys
 65                  70                  75                  80

Gly Ile Ile Ile Pro His Glu Asn Ser Pro Asp Gln Gln Gln Pro Glu
                 85                  90                  95

Glu His Arg Pro Lys Ile Gly Leu Ser Leu Lys Leu Gly Ala Ser Asn
            100                 105                 110

Ser Pro Gly Gln Pro Asn Ser Val Lys Arg Lys Lys Leu Pro Val Asp
        115                 120                 125

Ser Val Phe Asn Lys Phe Glu Asp Glu Asp Ser Asp Asp Val Pro Arg
    130                 135                 140

Lys Arg Lys Leu Val Pro Leu Asp Tyr Gly Glu Asp Asp Lys Asn Ala
145                 150                 155                 160

Thr Lys Gly Thr Val Asn Thr Glu Glu Lys Arg Lys His Ile Lys Ser
                165                 170                 175

Leu Ile Glu Lys Ile Pro Thr Ala Lys Pro Glu Leu Phe Ala Tyr Pro
            180                 185                 190

Leu Asp Trp Ser Ile Val Asp Ser Ile Leu Met Glu Arg Arg Ile Arg
        195                 200                 205

Pro Trp Ile Asn Lys Lys Ile Ile Glu Tyr Ile Gly Glu Glu Glu Ala
    210                 215                 220

Thr Leu Val Asp Phe Val Cys Ser Lys Val Met Ala His Ser Ser Pro
225                 230                 235                 240

Gln Ser Ile Leu Asp Asp Val Ala Met Val Leu Asp Glu Glu Ala Glu
                245                 250                 255

Val Phe Ile Val Lys Met Trp Arg Leu Leu Ile Tyr Glu Thr Glu Ala
            260                 265                 270

Lys Lys Ile Gly Leu Val Lys
        275
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3073 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..1111

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

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GC GGC CGC GCG CCG CAT TCG GAG AGC GGA CCC CAG AGA GCC CTG AGC
   Gly Arg Ala Pro His Ser Glu Ser Gly Pro Gln Arg Ala Leu Ser
    1               5                  10                  15

AGC CCC ACC GCC GCC GCC GGC CTA GTT ACC ATC ACA CCC CGG GAG GAG
Ser Pro Thr Ala Ala Ala Gly Leu Val Thr Ile Thr Pro Arg Glu Glu
             20                  25                  30

CCG CAG CTG CCG CAG CCG GCC CCA GTC ACC ATC ACC GCA ACC ATG AGC
Pro Gln Leu Pro Gln Pro Ala Pro Val Thr Ile Thr Ala Thr Met Ser
         35                  40                  45

AGC GAG GCC GAG ACC CAG CAG CCG CCC GCC GCC CCC CCC GCC GCC CCC
Ser Glu Ala Glu Thr Gln Gln Pro Pro Ala Ala Pro Pro Ala Ala Pro
     50                  55                  60

GCC CTC AGC GCC GCC GAC ACC AAG CCC GGC ACT ACG GGC AGC GGC GCA
Ala Leu Ser Ala Ala Asp Thr Lys Pro Gly Thr Thr Gly Ser Gly Ala
 65                  70                  75

GGG AGC GGT GGC CCG GGC GGC CTC ACA TCG GCG GCG CCT GCC GGC GGG
Gly Ser Gly Gly Pro Gly Gly Leu Thr Ser Ala Ala Pro Ala Gly Gly
80                  85                  90                  95

GAC AAG AAG GTC ATC GCA ACG AAG GTT TTG GGA ACA GTA AAA TGG TTC
Asp Lys Lys Val Ile Ala Thr Lys Val Leu Gly Thr Val Lys Trp Phe
                100                 105                 110

AAT GTA AGG AAC GGA TAT GGT TTC ATC AAC AGG AAT GAC ACC AAG GAA
Asn Val Arg Asn Gly Tyr Gly Phe Ile Asn Arg Asn Asp Thr Lys Glu
            115                 120                 125

GAT GTA TTT GTA CAC CAG ACT GCC ATA AAG AAG AAT AAC CCC AGG AAG
Asp Val Phe Val His Gln Thr Ala Ile Lys Lys Asn Asn Pro Arg Lys
        130                 135                 140

TAC CTT CGC AGT GTA GGA GAT GGA GAG ACT GTG GAG TTT GAT GTT GTT
Tyr Leu Arg Ser Val Gly Asp Gly Glu Thr Val Glu Phe Asp Val Val
    145                 150                 155

GAA GGA GAA AAG GGT GCG GAG GCA GCA AAT GTT ACA GGT CCT GGT GGT
Glu Gly Glu Lys Gly Ala Glu Ala Ala Asn Val Thr Gly Pro Gly Gly
160                 165                 170                 175
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GTT CCA GTT CAA GGC AGT AAA TAT GCA GCA GAC CGT AAC CAT TAT AGA
Val Pro Val Gln Gly Ser Lys Tyr Ala Ala Asp Arg Asn His Tyr Arg
180 185 190

CGC TAT CCA CGT CGT AGG GGT CCT CCA CGC AAT TAC CAG CAA AAT TAC
Arg Tyr Pro Arg Arg Arg Gly Pro Pro Arg Asn Tyr Gln Gln Asn Tyr
195 200 205

CAG AAT AGT GAG AGT GGG GAA AAG AAC GAG GGA TCG GAG AGT GCT CCC
Gln Asn Ser Glu Ser Gly Glu Lys Asn Glu Gly Ser Glu Ser Ala Pro
210 215 220

GAA GGC CAG GCC CAA CAA CGC CGG CCC TAC CGC AGG CGA AGG TTC CCA
Glu Gly Gln Ala Gln Gln Arg Arg Pro Tyr Arg Arg Arg Arg Phe Pro
225 230 235

CCT TAC TAC ATG CGG AGA CCC TAT GGG CGT CGA CCA CAG TAT TCC AAC
Pro Tyr Tyr Met Arg Arg Pro Tyr Gly Arg Arg Pro Gln Tyr Ser Asn
240 245 250 255

CCT CCT GTG CAG GGA GAA GTG ATG GAG GGT GCT GAC AAC CAG GGT GCA
Pro Pro Val Gln Gly Glu Val Met Glu Gly Ala Asp Asn Gln Gly Ala
260 265 270

GGA GAA CAA GGT AGA CCA GTG AGG CAG AAT ATG TAT CGG GGA TAT AGA
Gly Glu Gln Gly Arg Pro Val Arg Gln Asn Met Tyr Arg Gly Tyr Arg
275 280 285

CCA CGA TTC CGC AGG GGC CCT CCT CGC CAA AGA CAG CCT AGA GAG GAC
Pro Arg Phe Arg Arg Gly Pro Pro Arg Gln Arg Gln Pro Arg Glu Asp
290 295 300

GGC AAT GAA GAA GAT AAA GAA AAT CAA GGA GAT GAG ACC CAA GGT CAG
Gly Asn Glu Glu Asp Lys Glu Asn Gln Gly Asp Glu Thr Gln Gly Gln
305 310 315

CAG CCA CCT CAA CGT CGG TAC CGC CGC AAC TTC AAT TAC CGA CGC AGA
Gln Pro Pro Gln Arg Arg Tyr Arg Arg Asn Phe Asn Tyr Arg Arg Arg
320 325 330 335

CGC CCA GAA AAC CCT AAA CCA CAA GAT GGC AAA GAG ACA AAA GCA GCC
Arg Pro Glu Asn Pro Lys Pro Gln Asp Gly Lys Glu Thr Lys Ala Ala
340 345 350

GAT CCA CCA GCT GAG AAT TCG TCC GCT CCC GAG GCT GAG CAG GGC GGG
Asp Pro Pro Ala Glu Asn Ser Ser Ala Pro Glu Ala Glu Gln Gly Gly
355 360 365

GCT GAG TA AATGCCGGCT TACCATCTCT ACCATCATCC GGTTTAGTCA TCCAACAAGA
Ala Glu

AGAAATATGA AATTCCAGCA ATAAGAAATG AACAAAAGAT TGGAGCTGAA GACCTAAAGT
GCTTGCTTTT TGCCCGTTGA CCAGATAAAT AGAACTATCT GCATTATCTA TGCAGCATGG
GGTTTTTATT ATTTTTACCT AAAGACGTCT CTTTTTGGTA ATAACAAACG TGTTTTTTAA
AAAAGCCTGG TTTTTCTCAA TACGCCTTTA AAGGTTTTTA AATTGTTTCA TATCTGGTCA
AGTTGAGATT TTTAAGAACT TCATTTTTAA TTTGTAATAA AAGTTTACAA CTTGATTTTT
TCAAAAAAGT CAACAAACTG CAAGCACCTG TTAATAAAGG TCTTAAATAA TTGTCTTTGT
GTAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAG CTTGGTATTC ATTACTTCAT
GTATATCAAG CACAGCAGTA AAACAAAAAC CCATGTATTT AACTTTTTTT TAGGATTTTT
GCTTTTGTGA TTTTTTTTTT TTTTTTTTTG ATACTTGCCT AACATGCATG TGCTGTAAAA
ATAGTTAACA GGGAAATAAC TTGAGATGAT GGCTAGCTTT GTTTAATGTC TTATGAAATT
TTCATGAACA ATCCAAGCAT AATTGTTAAG AACACGTGTA TTAAATTCAT GTAAGTGGAA
TAAAAGTTTT ATGAATGGAC TTTTCAACTA CTTTCTCTAC AGCTTTTCAT GTAAATTAGT
CTTGGTTCTG AAACTTCTCT AAAGGAAATT GTACATTTTT TGAAATTTAT TCCTTATTCC
CTCTTGGCAG CTAATGGGCT CTTACCAAGT TTAAACACAA AATTTATCAT AACAAAAATA
CTACTAATAT AACTACTGTT TCCATGTCCC ATGATCCCCT CTCTTCCTCC CCACCCTGAA
AAAAATGAGT TCCTATTTTT TCTGGGAGAG GGGGGGATTG ATTAGAAAAA AATGTAGTGT
GTTCCATTTA AAATTTTGGC ATATGGCATT TTCTAACTTA GGAAGCCACA ATGTTCTTGG
CCCATCATGA CATTGGGTAG CATTAACTGT AAGTTTTGTG CTTCCAAATC ACTTTTTGGT
TTTTAAGAAT TTCTTGATAC TCTTATAGCC TGCCTTCAAT TTTGATCCTT TATTCTTTCT
ATTTGTCAGG TGCACAAGAT TACCTTCCTG TTTTAGCCTT CTGTCTTGTC ACCAACCATT
CTTACTTGGT GGCCATGTAC TTGGAAAAAG GCCGCATGAT CTTTCTGGCT CCACTCAGTG
TCTAAGGCAC CCTGCTTCCT TTGCTTGCAT CCCACAGACT ATTTCCCTCA TCCTATTTAC
TGCAGCAAAT CTCTCCTTAG TTGATGAGAC TGTGTTTATC TCCCTTTAAA ACCCTACCTA
TCCTGAATGG TCTGTCATTG TCTGCCTTTA AAATCCTTCC TCTTTCTTCC TCCTCTATTC
TCTAAATAAT GATGGGGCTA AGTTATACCC AAAGCTCACT TTACAAAATA TTTCCTCAGT
ACTTTGCAGA AAACACCAAA CAAAAATGCC ATTTTAAAAA AGGTGTATTT TTTCTTTTAG

AATGTAAGCT CCTCAAGAGC AGGGACAATG TTTTCTGTAT GTTCTATTGT GCCTAGTACA

CTGTAAATGC TCAATGAATA TTATCCCTAA TACCTGCCAC CCCACTCTTA ATCAGTGGTG

GAAGAACGGT CTCAGAACTG TTTGTTTCAA TTGGCCATTT AAGTTTAGTA GTAAAAGACT

GGTTAATGAT AACAATGCAT CGTAAAACCT TCAGAAGGAA AGGAGAATGT TTTGTGGACC

ACTTTGGTTT TCTTTTTTGC GTGTGGCAGT TTTAAGTTAT TAGTTTTTAA AATCAGTACT

TTTTAATGGA AACAACTTGA CCAAAAATTT GTCACAGAAT TTTGGCGGCC GC

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 369 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gly Arg Ala Pro His Ser Glu Ser Gly Pro Gln Arg Ala Leu Ser Ser
1 5 10 15

Pro Thr Ala Ala Ala Gly Leu Val Thr Ile Thr Pro Arg Glu Glu Pro
20 25 30

Gln Leu Pro Gln Pro Ala Pro Val Thr Ile Thr Ala Thr Met Ser Ser
35 40 45

Glu Ala Glu Thr Gln Gln Pro Pro Ala Ala Pro Pro Ala Ala Pro Ala
50 55 60

Leu Ser Ala Ala Asp Thr Lys Pro Gly Thr Thr Gly Ser Gly Ala Gly
65 70 75 80

Ser Gly Gly Pro Gly Gly Leu Thr Ser Ala Ala Pro Ala Gly Gly Asp
85 90 95

Lys Lys Val Ile Ala Thr Lys Val Leu Gly Thr Val Lys Trp Phe Asn
100 105 110

Val Arg Asn Gly Tyr Gly Phe Ile Asn Arg Asn Asp Thr Lys Glu Asp
115 120 125

Val Phe Val His Gln Thr Ala Ile Lys Lys Asn Asn Pro Arg Lys Tyr
130 135 140

Leu Arg Ser Val Gly Asp Gly Glu Thr Val Glu Phe Asp Val Val Glu
145 150 155 160

Gly Glu Lys Gly Ala Glu Ala Ala Asn Val Thr Gly Pro Gly Gly Val
165 170 175

Pro Val Gln Gly Ser Lys Tyr Ala Ala Asp Arg Asn His Tyr Arg Arg
180 185 190

Tyr Pro Arg Arg Arg Gly Pro Pro Arg Asn Tyr Gln Gln Asn Tyr Gln
195 200 205

Asn Ser Glu Ser Gly Glu Lys Asn Glu Gly Ser Glu Ser Ala Pro Glu
210 215 220

Gly Gln Ala Gln Gln Arg Arg Pro Tyr Arg Arg Arg Arg Phe Pro Pro
225 230 235 240

Tyr Tyr Met Arg Arg Pro Tyr Gly Arg Arg Pro Gln Tyr Ser Asn Pro
245 250 255

Pro Val Gln Gly Glu Val Met Glu Gly Ala Asp Asn Gln Gly Ala Gly
260 265 270

Glu Gln Gly Arg Pro Val Arg Gln Asn Met Tyr Arg Gly Tyr Arg Pro
275 280 285

Arg Phe Arg Arg Gly Pro Pro Arg Gln Arg Gln Pro Arg Glu Asp Gly
290 295 300

Asn Glu Glu Asp Lys Glu Asn Gln Gly Asp Glu Thr Gln Gly Gln Gln
305 310 315 320

Pro Pro Gln Arg Arg Tyr Arg Arg Asn Phe Asn Tyr Arg Arg Arg Arg
325 330 335

Pro Glu Asn Pro Lys Pro Gln Asp Gly Lys Glu Thr Lys Ala Ala Asp
340 345 350

Pro Pro Ala Glu Asn Ser Ser Ala Pro Glu Ala Glu Gln Gly Gly Ala
355 360 365

Glu

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1811 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GAATTCCTGG TAGGGCCAGC CCACCATGGG GGCCAAGACC TGCACAGGAC AAGGGCCACC
TGGCCTTTCA GTTACTTGAG TTTGGAGTCA GAAAGCAAGA CCAGGAAGCA AATAGCAGCT
CAGGAAATCC CACGGTTGAC TTGCCTTGAT GGCAAGCTTG GTGGAGAGGG CTGAAGCTGT
TGCTGGGGGC CGATTCTGAT CAAGACACAT GGCTTGAAAA TGGAAGACAC AAAACTGAGA
GATCATTCTG CACTAAGTTT CGGGAACTTA TCCCCGACAG TGACTGAACT CACTGACTAA
TAACTTCATT TATGAATCTT CTCCCTTGTC CCTTTGTCTG CCAACCTGTG TGCCTTTTTT
GTAAAACATT TTCATGTCTT TAAAATGCCT GTTGAATACC TGGAGTTTAG TATCAACTTC
TACACAGATA AGCTTTCAAA GTTGACAAAC TTTTTTGACT CTTTCTGGAA AAGGGAAAGA
AAATAGTCTT CCTTCTTTCT TGGGCAATAT CCTTCACTTT ACTACAGTTA CTTTTGCAAA
CAGACAGAAA GGATACACTT CTAACCACAT TTTACTTCCT TCCCCTGTTG TCCAGTCCAA
CTCCACAGTC ACTCTTAAAA CTTCTCTCTG TTTGCCTGCC TCCAACAGTA CTTTTAACTT
TTTGCTGTAA ACAGAATAAA ATTGAACAAA TTAGGGGGTA GAAAGGAGCA GTGGTGTCGT
TCACCGTGAG AGTCTGCATA GAACTCAGCA GTGTGCCCTG CTGTGTCTTG GACCCTGCCC
CCCACAGGAG TTGTACAGTC CCTGGCCCTG TTCCCTACCT CCTCTCTTCA CCCCGTTAGG
CTGTTTTCAA TGTAATGCTG CCGTCCTTCT CTTGCACTGC CTTCTGCGCT AACACCTCCA
TTCCTGTTTA TAACCGTGTA TTTATTACTT AATGTATATA ATGTAATGTT TTGTAAGTTA
TTAATTTATA TATCTAACAT TGCCTGCCAA TGGTGGTGTT AAATTTGTGT AGAAAACTCT
GCCTAAGAGT TACGACTTTT TCTTGTAATG TTTTGTATTG TGTATTATAT AACCCAAACG
TCACTTAGTA GAGACATATG GCCCCCTTGG CAGAGAGGAC AGGGGTGGGC TTTTGTTCAA
AGGGTCTGCC CTTTCCCTGC CTGAGTTGCT ACTTCTGCAC AACCCCTTTA TGAACCAGTT
TTGGAAACAA TATTCTCACA TTAGATACTA AATGGTTTAT ACTGAGCTTT TACTTTTGTA
TAGCTTGATA GGGGCAGGGG GCAATGGGAT GTAGTTTTTA CCCAGGTTCT ATCCAAATCT
ATGTGGGCAT GAGTTGGGTT ATAACTGGAT CCTACTATCA TTGTGGCTTT GGTTCAAAAG

GAAACACTAC ATTTGCTCAC AGATGATTCT TCTGAATGCT CCCGAACTAC TGACTTTGAA

GAGGTAGCCT CCTGCCTGCC ATTAAGCAGG AATGTCATGT TCCAGTTCAT TACAAAAGAA

AACAATAAAA CAATGTGAAT TTTTATAATA AAATGTGAAC TGATGTAGCA AATTACGCAA

ATGTGAAGCC TCTTCTGATA ACACTTGTTA GGCCTCTTAC TGATGTCAGT TTCAGTTTGT

AAAATATGTT TCATGCTTTC AGTTCAGCAT TGTGACTCAG TAATTACAGA AAATGGCACA

AATGTGCATG ACCAATGGGT TTGTATGTCT ATGAACACTG CATTGTTTCA GGTGGACATT

TTATCATTTT CAAATGTTTC TCACAATGTA TGTTATAGTA TTATTATTAT ATATTGTGTT

CAAATGCATT C

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1672 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GAATTCCCCA CCATGGGGGC CAAGACCTGC ACAGGACAAG GCCACCTGGC CTTTCAGTTA

CTTGAGTTTG GAGTCAGAAA GCAAGACCAG GAAGCAAATA GCAGCTCAGG AAATCCCACG

GTTGACTTGC CTTGATGGCA AGCTTGGTGG AGAGGGCTGA AGCTGTTGCT GGGGGCCGTT

CTGATCAAGA CACATGGCTT GAAAATGGAA GACACAAAAC TGAGAGATCA TTCTGCACTA

AGTTTCGGGA ACTTATCCCC GACAGTGACT GAACTCACTG ACTAATAACT TCATTTATGA

ATCTTCTCCC TTGTCCCTTT GTCTGCCAAC CTGTGTGCCT TTTTTGTAAA ACATTTCAGT

CTTTAAAATG CCTGTTGAAT ACCTGGAGTT AGATCAACTT CTACACAGAT AAGCTTTCAA

AGTTGACAAA CTTTTTTGAC TCTTCTGGAA AAGGGAAAGA AAATAGTCTT CCTTCTTTCT

TGGGCAATAT CCTTCACTTT ACTACAGTTA CTTTTGCAAA CAGACAGAAA GGATACACTT

CTAACCACAT TTTACTTCCT TCCCCTGTTG TCCAGTCCAA CTCCACAGTC ACTCTTAAAA

CTTCTCTCTG TTTGCCTGCC TCCAACAGTA CTTTTAACTT TTAACTTTTT GCTGTAAACA

GAATAAAATT GAACAAATTA GGGGGTAGAA AGGAGCAGTG GTGTCGTTCA CCGTGAGAGT
CTGCATAGAA CTCAGCAGTG TGCCCTGCTG TGTCTTGGAC CCTGCCCCCC ACAGGAGTTG
TACAGTCCCT GGCCCTGTTC CCTACCTCCT CTCTTCACCC CGTTAGGCTG TTTTCAATGT
AATGCTGCCG TCCTTCTCTT GCACTGCCTT CTGCGCTAAC ACCTCCATTC CTGTTTATAA
CCGTGTATTT ATTACTTAAT GTATATAATG TAATGTTTTG TAAGTTATTA ATTTATATAT
CTAACATTGC CTGCCAATGG TGGTGTTAAA TTTGTGTAGA AAACTCTGCC TAAGAGTTAC
GACTTTTTCT TGTAATGTTT TGTATTGTGT ATTATATAAC CCAAACGTCA CTTAGTAGAG
ACATATGGCC CCCTTGGCAG AGAGGACAGG GGTGGGCTTT TGTTCAAAGG GTCTGCCCTT
TCCCTGCCTG AGTTGCTACT TCTGCACAAC CCCTTTATGA ACCAGTTTTG GAAACAATAT
TCTCACATTA GATACTAAAT GGTTTATACT GAGCTTTTAC TTTTGTATAG CTTGATAGGG
GCAGGGGGCA ATGGGATGTA GTTTTTACCC AGGTTCTATC CAAATCTATG TGGGCATGAG
TTGGGTTATA ACTGGATCCT ACTATCATTG TGGCTTTGGT TCAAAAGGAA ACACTACATT
TGCTCACAGA TGATTCTTCT GAATGCTCCC GAACTACTGA CTTTGAAGAG GTAGCCTCCT
GCCTGCCATT AAGCAGGAAT GTCATGTTCC AGTTCATTAC AAAAGAAAAC AATAAAACAA
TGTGAATTTT TATAATAAAA TGTGAACTGA TGTAGCAAAT TACGCAAATG TGAAGCCTCT
TCTGATAACA CTTGTTAGGC CTCTTACTGA TGTCAGTTTC AGTTTGTAAA ATATGTTTCA
TGCTTTCAGT TCAGCATTGT GACTCAGTAA TTACAGAAAA AAAAAAGAAT TC

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1649 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 210..1018

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GAATTCCTTC TGACGTGGCA TATCACAACA GCCTGCACGC TGCTGATGTA GCCCAGTCGA

CCCATGTTCT CCTTTCTACA CCAGCATTAG ACGCTGTCTT CACAGATTTG GAAATCCTGG

CTGCCATTTT TGCAGCTGCC ATCCATGACG TTGATCATCC TGGAGTCTCC AATCAGTTTC

TCATCAACAC AAATTCAGAA CTTGCTTTG ATG TAT AAT GAT GAA TCT GTG TTG
Met Tyr Asn Asp Glu Ser Val Leu
1 5

GAA AAT CAT CAC CTT GCT GTG GGT TTC AAA CTG CTG CAA GAA GAA CAC
Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His
10 15 20

TGT GAC ATC TTC ATG AAT CTC ACC AAG AAG CAG CGT CAG ACA CTC AGG
Cys Asp Ile Phe Met Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg
25 30 35 40

AAG ATG GTT ATT GAC ATG GTG TTA GCA ACT GAT ATG TCT AAA CAT ATG
Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met
45 50 55

AGC CTG CTG GCA GAC CTG AAG ACA ATG GTA GAA ACG AAG AAA GTT ACA
Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr
60 65 70

AGT TCA GGC GTT CTT CTC CTA GAC AAC TAT ACC GAT CGC ATT CAG GTC
Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val
75 80 85

CTT CGC AAC ATG GTA CAC TGT GCA GAC CTG AGC AAC CCC ACC AAG TCC
Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser
90 95 100

TTG GAA TTG TAT CGG CAA TGG ACA GAC CGC ATC ATG GAG GAA TTT TTC
Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe
105 110 115 120

CAG CAG GGA GAC AAA GAG CGG GAG AGG GGA ATG GAA ATT AGC CCA ATG
Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met
125 130 135

TGT GAT AAA CAC ACA GCT TCT GTG GAA AAA TCC CAG GTT GGT TTC ATC
Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile
140 145 150

GAC TAC ATT GTC CAT CCA TTG TGG GAG ACA TGG GCA GAT TTG GTA CAG
Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln
155 160 165

CCT GAT GCT CAG GAC ATT CTC GAT ACC TTA GAA GAT AAC AGG AAC TGG

Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp
    170   175   180

TAT CAG AGC ATG ATA CCT CAA AGT CCC TCA CCA CCA CTG GAC GAG CAG
Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Gln
185   190   195   200

AAC AGG GAC TGC CAG GGT CTG ATG GAG AAG TTT CAG TTT GAA CTG ACT
Asn Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr
                205   210   215

CTC GAT GAG GAA GAT TCT GAA GGA CCT GAG AAG GAG GGA GAG GGA CAC
Leu Asp Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His
            220   225   230

AGC TAT TTC AGC AGC ACA AAG ACG CTT TGT GTG ATT GAT CCA GAA AAC
Ser Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn
        235   240   245

AGA GAT TCC CTG GGA GAG ACT GAC ATA GAC ATT GCA ACA GAA GAC AAG
Arg Asp Ser Leu Gly Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys
    250   255   260

TCC CCC GTG GAT ACA TA ATCCCCCTCT CCCTGTGGAG ATGAACATTC
Ser Pro Val Asp Thr
265

TATCCTTGAT GAGCATGCCA GCTATGTGGT AGGGCCAGCC CACCATGGGG GCCAAGACCT

GCACAGGACA AGGGCCACCT GGCCTTTCAG TTACTTGAGT TTGGAGTCAG AAAGCAAGAC

CAGGAAGCAA ATAGCAGCTC AGGAAATCCC ACGGTTGACT TGCCTTGATG GCAAGCTTGG

TGGAGAGGGC TGAAGCTGTT GCTGGGGGCC GATTCTGATC AAGACACATG GCTTGAAAAT

GGAAGACACA AAACCGAGAG ATCATTCTGC ACTAAGTTTC GGGAACTTAT CCCCGACAGT

GACTGAACTC ACTGACTAAT AACTTCATTT ATGAATCTTC TCCCTTGTCC CTTTGTCTGC

CAACCTGTGT GCCTTTTTTG TAAAACATTT TCATGTCTTT AAAATGCCTG TTGAATACCT

GGAGTTTAGT ATCAACTTCT ACACAGATAA GCTTTCAAAG TTGACAAACT TTTTTGACTC

TTTCTGGAAA AGGGAAAGAA AATAGTCTTC CTTCTTTCTT GGGCAATATC CTTCACTTTA

CTACAGTTAC TTTTGCAAAC AGACAGAAAG GATACACTTC TAACCACATT TTACGGAATT

C

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 269 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu Ala Val Gly
 1              5                  10                  15

Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Met Asn Leu Thr
            20                  25                  30

Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp Met Val Leu
        35                  40                  45

Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp Leu Lys Thr
    50                  55                  60

Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp
65                  70                  75                  80

Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val His Cys Ala
                85                  90                  95

Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr
            100                 105                 110

Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu
        115                 120                 125

Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser Val
    130                 135                 140

Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp
145                 150                 155                 160

Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp Ile Leu Asp
                165                 170                 175

Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser
            180                 185                 190

Pro Ser Pro Pro Leu Asp Glu Gln Asn Arg Asp Cys Gln Gly Leu Met
        195                 200                 205

Glu Lys Phe Gln Phe Glu Leu Thr Leu Asp Glu Glu Asp Ser Glu Gly
    210                 215                 220

Pro Glu Lys Glu Gly Glu Gly His Ser Tyr Phe Ser Ser Thr Lys Thr
```

```
225                 230                 235                 240

Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Gly Glu Thr Asp
                245                 250                 255

Ile Asp Ile Ala Thr Glu Asp Lys Ser Pro Val Asp Thr
            260                 265
```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 609 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..606

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
G AAT TCC AAC ATT CCC CGA TTT GGG GTG AAG ACC GAT CAA GAA GAG
  Asn Ser Asn Ile Pro Arg Phe Gly Val Lys Thr Asp Gln Glu Glu
    1               5                  10                  15

CTC CTG GCC CAA GAA CTG GAG AAC CTG AAC AAG TGG GGC CTG AAC ATC
Leu Leu Ala Gln Glu Leu Glu Asn Leu Asn Lys Trp Gly Leu Asn Ile
                20                  25                  30

TTT TGC GTG TCG GAT TAC GCT GGA GGC CGC TCA CTC ACC TGC ATC ATG
Phe Cys Val Ser Asp Tyr Ala Gly Gly Arg Ser Leu Thr Cys Ile Met
            35                  40                  45

TAC ATG ATA TTC CAG GAG CGG GAC CTG CTG AAG AAA TTC CGC ATC CCT
Tyr Met Ile Phe Gln Glu Arg Asp Leu Leu Lys Lys Phe Arg Ile Pro
        50                  55                  60

GTG GAC ACG ATG GTG ACA TAC ATG CTG ACG CTG GAG GAT CAC TAC CAC
Val Asp Thr Met Val Thr Tyr Met Leu Thr Leu Glu Asp His Tyr His
    65                  70                  75

GCT GAC GTG GCC TAC CAT AAC AGC CTG CAC GCA GCT GAC GTG CTG CAG
Ala Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Leu Gln
80                  85                  90                  95

TCC ACC CAC GTA CTG CTG GCC ACG CCT GCA CTA GAT GCA GTG TTC ACG
Ser Thr His Val Leu Leu Ala Thr Pro Ala Leu Asp Ala Val Phe Thr
```

```
                    100                 105                 110

GAC CTG GAG ATT CTC GCC GCC CTC TTC GCG GCT GCC ATC CAC GAT GTG
Asp Leu Glu Ile Leu Ala Ala Leu Phe Ala Ala Ala Ile His Asp Val
            115                 120                 125

GAT CAC CCT GGG GTC TCC AAC CAG TTC CTC ATC AAC ACC AAT TCG GAG
Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
        130                 135                 140

CTG GCG CTC ATG TAC AAC GAT GAG TCG GTG CTC GAG AAT CAC CAC CTG
Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
    145                 150                 155

GCC GTG GGC TTC AAG CTG CTG CAG GAG GAC AAC TGC GAC ATC TTC CAG
Ala Val Gly Phe Lys Leu Leu Gln Glu Asp Asn Cys Asp Ile Phe Gln
160                 165                 170                 175

AAC CTC AGC AAG CGC CAG CGG CAG AGC TAC GCA AGA TGG TCA TCG ACA
Asn Leu Ser Lys Arg Gln Arg Gln Ser Tyr Ala Arg Trp Ser Ser Thr
                180                 185                 190

TGG TGC TGG CCA CGG ACA TGT CCA AGC ACA TG ACC
Trp Cys Trp Pro Arg Thr Cys Pro Ser Thr
            195                 200
```

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 201 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
Asn Ser Asn Ile Pro Arg Phe Gly Val Lys Thr Asp Gln Glu Glu Leu
1               5                   10                  15

Leu Ala Gln Glu Leu Glu Asn Leu Asn Lys Trp Gly Leu Asn Ile Phe
            20                  25                  30

Cys Val Ser Asp Tyr Ala Gly Gly Arg Ser Leu Thr Cys Ile Met Tyr
        35                  40                  45

Met Ile Phe Gln Glu Arg Asp Leu Leu Lys Lys Phe Arg Ile Pro Val
    50                  55                  60

Asp Thr Met Val Thr Tyr Met Leu Thr Leu Glu Asp His Tyr His Ala
65                  70                  75                  80
```

Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Leu Gln Ser
85 90 95

Thr His Val Leu Leu Ala Thr Pro Ala Leu Asp Ala Val Phe Thr Asp
100 105 110

Leu Glu Ile Leu Ala Ala Leu Phe Ala Ala Ala Ile His Asp Val Asp
115 120 125

His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu Leu
130 135 140

Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu Ala
145 150 155 160

Val Gly Phe Lys Leu Leu Gln Glu Asp Asn Cys Asp Ile Phe Gln Asn
165 170 175

Leu Ser Lys Arg Gln Arg Gln Ser Tyr Ala Arg Trp Ser Ser Thr Trp
180 185 190

Cys Trp Pro Arg Thr Cys Pro Ser Thr
195 200

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1229 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ACATGGTGCA CTGTGCCGAC CTCAGCAACC CCACCAAGCC GCTGGAGCTG TACCGCCAGT

GGACAGACCG CATCATGGCC GAGTTCTTCC AGCAGGGTGA CCGAGAGCGC GAGCGTGGCA

TGGAAATCAG CCCCATGTGT GACAAGCACA CTGCCTCCGT GGAGAAGTCT CAGGTGGGTT

TTATTGACTA CATTGTGCAC CCATTGTGGG AGACCTGGGC GGACCTTGTC CACCCAGATG

CCCAGGAGAT CTTGGACACT TTGGAGGACA ACCGGGACTG GTACTACAGC GCCATCCGGC

AGAGCCCATC TCCGCCACCC GAGGAGGAGT CAAGGGGGCC AGGCCACCCA CCCCTGCCTG

ACAAGTTCCA GTTTGACGTG ACGCTGGAGG AGGAAGAGGA GGAAGAAATA TCAATGGCCC
AGATACCGTG CACAGCCCAA GAGGCATTGA CTGCGCAGGG ATTGTCAGGA GTCGAGGAAG
CTCTGGATGC AACCATAGCC TGGGAGGCAT CCCCGGCCCA GGAGTCGTTG GAAGTTATGG
CACAGGAAGC ATCCCTGGAG GCCGAGCTGG AGGCAGGTAT TTGACACAGC AGGCACAGTC
CACAGGCAGT GCACCTGTGG CTCCGGATGA GTTCTCGTCC CGGGAGGAAT TCGTGGTTGC
TGTAAGCCAC AGCAGCCCCT CTGCCCTGGC TCTTCAAAGC CCCCTTCTCC CTGCTTGGAG
GACCCTGTCT GTTTCAGAGC ATGCCCCGGG CCTCCCGGCC TCCCCTCCAC GGCGGCCTAG
GTGGAACGAG AGCACCAGGC TGCCAAGAGG GCTTGCAGTG CCTGCGCAGG GACATTTGGG
GAGGACACAT CCGCACTCCC AGCTCCTGGT GGCGGGGGGT CAGGTGGAGA CCCTACCTGA
TCCCCAGACC TCTGTCCCTG TTCCCCTCCA CTCCTCCCCT CACTCCCCTG CTCCCCCGAC
CACCTCCTCC TCTGCCTCAA AGACTCTTGT CCTCTTGTCC CTCCTGAGAA AAAAGAAAAC
GAAAAGTGGG GTTTTTTTCT GTTTTCTTTT TTTCCCCTTT CCCCCTGCCC CCACCCACGG
GGCCTTTTTT TGGAGGTGGG GGCTGGGGAA TGAGGGGCTG AGGTCCCGGA AGGGATTTTA
TTTTTTTGAA TTTTAATTGT AACATTTTTA GAAAAAGAAC AAAAAAAGAA AAAAAAAAGA
AAGAAACACA AAAAAAAAAA AAGGAATTC

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 798 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GAATTCCTCT GACTAATTCA AGTATCCCAA GGTTTGGAGT TAAAACTGAA CAAGAAGATG
TCCTTGCCAA GGAACTAGAA GATGTGAACA AATGGGGTCT TCATGTTTTC AGAATAGCAG
AGTTGTCTGG TAACCGGCCC TTGACTGTTA TCATGCACAC CATTTTTCAG GAACGGGATT
TATTAAAAAC ATTTAAAATT CCAGTAGATA CTTTAATTAC ATATCTTATG ACTCTCGAAG

```
ACCATTACCA TGCTGATGTG GCCTATCACA ACAATATCCA TGCTGCAGAT GTTGTCCAGT

CTACTCATGT GCTATTATCT ACACCTGCTT TGGAGGCTGT GTTTACAGAT TTGGAGATTC

TTGCAGCAAT TTTTGCCAGT GCAATACATG ATGTAGATCA TCCTGGTGTG TCCAATCAAT

TTCTGATCAA TACAAACTCT GAACTTGCCT TGATGTACAA TGATTCCTCA GTCTTAGAGA

ACCATCATTT GGCTGTGGGC TTTAAATTGC TTCAGGAAGA AAACTGTGAC ATTTTCCAGA

ATTTGACCAA AAAACAAAGA CAATCTTTAA GGAAAATGGT CATTGACATC GTACTTGCAA

CAGATATGTC AAAACACATG AATCTACTGG CTGATTTGAA GACTATGGTT GAAACTAAGA

AAGTGACAAG CTCTGGAGTT CTTCTTCTTG ATAATTATTC CGATAGGATT CAGGTTCTTC

AGAATATGGT GCACTGTGCA GATCTGAGCA ACCCAACAAA GCCTCTCCAG CTGTACCGCC

AGTGGACGGA CGGAATTC
```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1902 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 97..1256

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```
GAATTCCTTT GTTCACATCT TCTAGTTCCT TGGCAAGGAC ATCTTCATGT TTTCAGAATA

GCAGAGTTGT CTGGTAACCG GCCCTTGACT GTTATC ATG CAC ACC ATT TTT CAG
                                       Met His Thr Ile Phe Gln
                                        1               5

GAA CGG GAT TTA TTA AAA ACA TTT AAA ATT CCA GTA GAT ACT TTA ATT
Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Pro Val Asp Thr Leu Ile
             10                  15                  20

ACA TAT CTT ATG ACT CTC GAA GAC CAT TAC CAT GCT GAT GTG GCC TAT
Thr Tyr Leu Met Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr
         25                  30                  35
```

```
CAC AAC AAT ATC CAT GCT GCA GAT GTT GTC CAG TCT ACT CAT GTG CTA
His Asn Asn Ile His Ala Ala Asp Val Val Gln Ser Thr His Val Leu
     40                  45                      50

TTA TCT ACA CCT GCT TTG GAG GCT GTG TTT ACA GAT TTG GAG ATT CTT
Leu Ser Thr Pro Ala Leu Glu Ala Val Phe Thr Asp Leu Glu Ile Leu
 55                  60                  65                  70

GCA GCA ATT TTT GCC AGT GCA ATA CAT GAT GTA GAT CAT CCT GGT GTG
Ala Ala Ile Phe Ala Ser Ala Ile His Asp Val Asp His Pro Gly Val
                 75                  80                  85

TCC AAT CAA TTT CTG ATC AAT ACA AAC TCT GAA CTT GCC TTG ATG TAC
Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr
             90                  95                 100

AAT GAT TCC TCA GTC TTA GAG AAC CAT CAT TTG GCT GTG GGC TTT AAA
Asn Asp Ser Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys
        105                 110                 115

TTG CTT CAG GAA GAA AAC TGT GAC ATT TTC CAG AAT TTG ACC AAA AAA
Leu Leu Gln Glu Glu Asn Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys
    120                 125                 130

CAA AGA CAA TCT TTA AGG AAA ATG GTC ATT GAC ATC GTA CTT GCA ACA
Gln Arg Gln Ser Leu Arg Lys Met Val Ile Asp Ile Val Leu Ala Thr
135                 140                 145                 150

GAT ATG TCA AAA CAC ATG AAT CTA CTG GCT GAT TTG AAG ACT ATG GTT
Asp Met Ser Lys His Met Asn Leu Leu Ala Asp Leu Lys Thr Met Val
                155                 160                 165

GAA ACT AAG AAA GTG ACA AGC TCT GGA GTT CTT CTT CTT GAT AAT TAT
Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr
            170                 175                 180

TCC GAT AGG ATT CAG GTT CTT CAG AAT ATG GTG CAC TGT GCA GAT CTG
Ser Asp Arg Ile Gln Val Leu Gln Asn Met Val His Cys Ala Asp Leu
        185                 190                 195

AGC AAC CCA ACA AAG CCT CTC CAG CTG TAC CGC CAG TGG ACG GAC CGG
Ser Asn Pro Thr Lys Pro Leu Gln Leu Tyr Arg Gln Trp Thr Asp Arg
    200                 205                 210

ATA ATG GAG GAG TTC TTC CGC CAA GGA GAC CGA GAG AGG GAA CGT GGC
Ile Met Glu Glu Phe Phe Arg Gln Gly Asp Arg Glu Arg Glu Arg Gly
215                 220                 225                 230

ATG GAG ATA AGC CCC ATG TGT GAC AAG CAC AAT GCT TCC GTG GAA AAA
Met Glu Ile Ser Pro Met Cys Asp Lys His Asn Ala Ser Val Glu Lys
                235                 240                 245
```

TCA CAG GTG GGC TTC ATA GAC TAT ATT GTT CAT CCC CTC TGG GAG ACA
Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr
250 255 260

TGG GCA GAC CTC GTC CAC CCT GAC GCC CAG GAT ATT TTG GAC ACT TTG
Trp Ala Asp Leu Val His Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu
265 270 275

GAG GAC AAT CGT GAA TGG TAC CAG AGC ACA ATC CCT CAG AGC CCC TCT
Glu Asp Asn Arg Glu Trp Tyr Gln Ser Thr Ile Pro Gln Ser Pro Ser
280 285 290

CCT GCA CCT GAT GAC CCA GAG GAG GGC CGG CAG GGT CAA ACT GAG AAA
Pro Ala Pro Asp Asp Pro Glu Glu Gly Arg Gln Gly Gln Thr Glu Lys
295 300 305 310

TTC CAG TTT GAA CTA ACT TTA GAG GAA GAT GGT GAG TCA GAC ACG GAA
Phe Gln Phe Glu Leu Thr Leu Glu Glu Asp Gly Glu Ser Asp Thr Glu
315 320 325

AAG GAC AGT GGC AGT CAA GTG GAA GAA GAC ACT AGC TGC AGT GAC TCC
Lys Asp Ser Gly Ser Gln Val Glu Glu Asp Thr Ser Cys Ser Asp Ser
330 335 340

AAG ACT CTT TGT ACT CAA GAC TCA GAG TCT ACT GAA ATT CCC CTT GAT
Lys Thr Leu Cys Thr Gln Asp Ser Glu Ser Thr Glu Ile Pro Leu Asp
345 350 355

GAA CAG GTT GAA GAG GAG GCA GTA GGG GAA GAA GAG GAA AGC CAG CCT
Glu Gln Val Glu Glu Glu Ala Val Gly Glu Glu Glu Glu Ser Gln Pro
360 365 370

GAA GCC TGT GTC ATA GAT GAT CGT TCT CCT GAC ACG TA ACAGTGCAAA
Glu Ala Cys Val Ile Asp Asp Arg Ser Pro Asp Thr
375 380 385

AACTTTCATG CCTTTTTTTT TTTTAAGTAG AAAAATTGTT TCCAAAGTGC ATGTCACATG

CCACAACCAC GGTCACACCT CACTGTCATC TGCCAGGACG TTTGTTGAAC AAAACTGACC

TTGACTACTC AGTCCAGCGC TCAGGAATAT CGTAACCAGT TTTTTCACCT CCATGTCATC

CGAGCAAGGT GGACATCTTC ACGAACAGCG TTTTTAACAA GATTTCAGCT TGGTAGAGCT

GACAAAGCAG ATAAAATCTA CTCCAAATTA TTTTCAAGAG AGTGTGACTC ATCAGGCAGC

CCAAAAGTTT ATTGGACTTG GGGTTTCTAT TCCTTTTTAT TTGTTTGCAA TATTTTCAGA

AGAAAGGCAT TGCACAGAGT GAACTTAATG GACGAAGCAA CAAATATGTC AAGAACAGGA

CATAGCACGA ATCTGTTACC AGTAGGAGGA GGATGAGCCA CAGAAATTGC ATAATTTTCT

AATTTCAAGT CTTCCTGATA CATGACTGAA TAGTGTGGTT CAGTGAGCTG CACTGACCTC

TACATTTTGT ATGATATGTA AAACAGATTT TTTGTAGAGC TTACTTTTAT TATTAAATGT

ATTGAGGTAT TATATTTAAA AAAAAAAAAG GAATTC

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 386 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Met His Thr Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile
1 5 10 15

Pro Val Asp Thr Leu Ile Thr Tyr Leu Met Thr Leu Glu Asp His Tyr
20 25 30

His Ala Asp Val Ala Tyr His Asn Asn Ile His Ala Ala Asp Val Val
35 40 45

Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Glu Ala Val Phe
50 55 60

Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ser Ala Ile His Asp
65 70 75 80

Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser
85 90 95

Glu Leu Ala Leu Met Tyr Asn Asp Ser Ser Val Leu Glu Asn His His
100 105 110

Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu Asn Cys Asp Ile Phe
115 120 125

Gln Asn Leu Thr Lys Lys Gln Arg Gln Ser Leu Arg Lys Met Val Ile
130 135 140

Asp Ile Val Leu Ala Thr Asp Met Ser Lys His Met Asn Leu Leu Ala
145 150 155 160

Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val
165 170 175

```
Leu Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Gln Asn Met
            180                 185                 190

Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Gln Leu Tyr
        195                 200                 205

Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Arg Gln Gly Asp
    210                 215                 220

Arg Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His
225                 230                 235                 240

Asn Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val
                245                 250                 255

His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp Ala Gln
            260                 265                 270

Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr Gln Ser Thr
        275                 280                 285

Ile Pro Gln Ser Pro Ser Pro Ala Pro Asp Asp Pro Glu Glu Gly Arg
    290                 295                 300

Gln Gly Gln Thr Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Asp
305                 310                 315                 320

Gly Glu Ser Asp Thr Glu Lys Asp Ser Gly Ser Gln Val Glu Glu Asp
                325                 330                 335

Thr Ser Cys Ser Asp Ser Lys Thr Leu Cys Thr Gln Asp Ser Glu Ser
            340                 345                 350

Thr Glu Ile Pro Leu Asp Glu Gln Val Glu Glu Glu Ala Val Gly Glu
        355                 360                 365

Glu Glu Glu Ser Gln Pro Glu Ala Cys Val Ile Asp Asp Arg Ser Pro
    370                 375                 380

Asp Thr
385
```

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1155 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 95..762

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
GAATTCCCTG GCTGTGGGCT TCAAGCTGCT GCAGGCAGAG AACTGCGATA TCTTCCAGAA

CCTCAGCGCC AAGCAGCGAC TGAGTCTGCG CAGG ATG GTC ATT GAC ATG GTG
                                      Met Val Ile Asp Met Val
                                       1               5

CTG GCC ACA GAC ATG TCC AAA CAC ATG AAC CTC CTG GCC GAC CTC AAG
Leu Ala Thr Asp Met Ser Lys His Met Asn Leu Leu Ala Asp Leu Lys
             10                  15                  20

ACC ATG GTG GAG ACC AAG AAG GTG ACA AGC CTC GGT GTC CTC CTC CTG
Thr Met Val Glu Thr Lys Lys Val Thr Ser Leu Gly Val Leu Leu Leu
         25                  30                  35

GAC AAC TAT TCC GAC CGA ATC CAG GTC TTG CAG AAC CTG GTG CAC TGT
Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Gln Asn Leu Val His Cys
     40                  45                  50

GCT GAT CTG AGC AAC CCC ACC AAG CCG CTG CCC CTG TAC CGC CAG TGG
Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Pro Leu Tyr Arg Gln Trp
 55                  60                  65                  70

ACG GAC CGC ATC ATG GCC GAG TTC TTC CAG CAG GGA GAC CGC GAG CGT
Thr Asp Arg Ile Met Ala Glu Phe Phe Gln Gln Gly Asp Arg Glu Arg
                 75                  80                  85

GAG TCG GGC CTG GAC ATC AGT CCC ATG TGT GAC AAG CAT ACG GCC TCA
Glu Ser Gly Leu Asp Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser
             90                  95                 100

GTG GAG AAG TCC CAG GTG GGT TTC ATT GAC TAC ATT GCT CAC CCA CTG
Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Ala His Pro Leu
        105                 110                 115

TGG GAG ACT TGG GCT GAC CTG GTC CAC CCA GAT GCA CAG GAC CTG CTG
Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp Ala Gln Asp Leu Leu
    120                 125                 130

GAC ACG CTG GAG GAC AAT CGA GAG TGG TAC CAG AGC AAG ATC CCC CGA
Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr Gln Ser Lys Ile Pro Arg
135                 140                 145                 150

AGT CCC TCA GAC CTC ACC AAC CCC GAG CGG GAC GGG CCT GAC AGA TTC
Ser Pro Ser Asp Leu Thr Asn Pro Glu Arg Asp Gly Pro Asp Arg Phe
```

155 160 165

CAG TTT GAA CTG ACT CTG GAG GAG GCA GAG GAA GAG GAT GAG GAG GAA
Gln Phe Glu Leu Thr Leu Glu Glu Ala Glu Glu Glu Asp Glu Glu Glu
170 175 180

GAA GAG GAG GGG GAA GAG ACA GCT TTA GCC AAA GAG GCC TTG GAG TTG
Glu Glu Glu Gly Glu Glu Thr Ala Leu Ala Lys Glu Ala Leu Glu Leu
185 190 195

CCT GAC ACT GAA CTC CTG TCC CCT GAA GCC GGC CCA GAC CCT GGG GAC
Pro Asp Thr Glu Leu Leu Ser Pro Glu Ala Gly Pro Asp Pro Gly Asp
200 205 210

TTA CCC CTC GAC AAC CAG AGG ACT TA GGGCCAGCCC TGCGTGAACT
Leu Pro Leu Asp Asn Gln Arg Thr
215 220

GCAGGGGCAA TGGATGGTAA AGCCCTTTGG CTCTTGGCAG GCAGACTTTC CAGGAAGAGG

CTCCATGTGG CTCCTGCTTC ACTTTCCCAC CCATTTAGGG AGACAATCAA GCTCTTAGTT

ATAGGTGGCT CCCAGGGTCT AATTGGAGGC ACCTGGCTGG GGTCCACTCT GACCCTAGAC

TTGCCTAAAA GAGCTCTCTA AGGGGCAGCC TCTTACGATG CCCTGGTGTC TTTCTCCTGG

GCTTCTATCC CTGTGAGGAG AGGTGCTGTC TGCTGGAGCC TCTAGTCCAC CCTCTCCAGT

GGTCACTCTT GAGTCACATC TGTCACTTAA TTATTTCCTT CTTTATCAAA TATTTATTGC

TCATCTGGAA TTC

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 222 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Asn
1 5 10 15

Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser
20 25 30

Leu Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu
35 40 45

```
Gln Asn Leu Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu
    50                  55                  60

Pro Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Ala Glu Phe Phe Gln
65                  70                  75                  80

Gln Gly Asp Arg Glu Arg Glu Ser Gly Leu Asp Ile Ser Pro Met Cys
                85                  90                  95

Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp
            100                 105                 110

Tyr Ile Ala His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro
        115                 120                 125

Asp Ala Gln Asp Leu Leu Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr
    130                 135                 140

Gln Ser Lys Ile Pro Arg Ser Pro Ser Asp Leu Thr Asn Pro Glu Arg
145                 150                 155                 160

Asp Gly Pro Asp Arg Phe Gln Phe Glu Leu Thr Leu Glu Glu Ala Glu
                165                 170                 175

Glu Glu Asp Glu Glu Glu Glu Glu Glu Gly Glu Glu Thr Ala Leu Ala
            180                 185                 190

Lys Glu Ala Leu Glu Leu Pro Asp Thr Glu Leu Leu Ser Pro Glu Ala
        195                 200                 205

Gly Pro Asp Pro Gly Asp Leu Pro Leu Asp Asn Gln Arg Thr
    210                 215                 220
```

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TACGAAGCTT TGATGGGGTC TACTGCTAC

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TACGAAGCTT TGATGGTTGG CTTGGCATAT C

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

ATTAACCCTC ATAAAG

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TACGAAGCTT TGATGCGCCG ACAGCCTGC

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GGTCTCCTGT TGCAGATATT G

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TTYAARTCTN YTNCARGRNG A

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

ACNATRTCTR ATNACCATYT T

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Phe Lys Leu Leu Gln Glu Glu Asn
1 5

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
Phe Lys Leu Leu Gln Gly Glu Asn
1               5
```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1155 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 95..762

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
GAATTCCCTG GCTGTGGGCT TCAAGCTGCT GCAGGCAGAG AACTGCGATA TCTTCCAGAA

CCTCAGCGCC AAGCAGCGAC TGAGTCTGCG CAGG ATG GTC ATT GAC ATG GTG
                                      Met Val Ile Asp Met Val
                                      1                   5

CTG GCC ACA GAC ATG TCC AAA CAC ATG AAC CTC CTG GCC GAC CTC AAG
Leu Ala Thr Asp Met Ser Lys His Met Asn Leu Leu Ala Asp Leu Lys
            10                  15                  20

ACC ATG GTG GAG ACC AAG AAG GTG ACA AGC CTC GGT GTC CTC CTC CTG
Thr Met Val Glu Thr Lys Lys Val Thr Ser Leu Gly Val Leu Leu Leu
        25                  30                  35

GAC AAC TAT TCC GAC CGA ATC CAG GTC TTG CAG AAC CTG GTG CAC TGT
Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Gln Asn Leu Val His Cys
    40                  45                  50

GCT GAT CTG AGC AAC CCC ACC AAG CCG CTG CCC CTG TAC CGC CAG TGG
Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Pro Leu Tyr Arg Gln Trp
55                  60                  65                  70

ACG GAC CGC ATC ATG GCC GAG TTC TTC CAG CAG GGA GAC CGC GAG CGT
Thr Asp Arg Ile Met Ala Glu Phe Phe Gln Gln Gly Asp Arg Glu Arg
```

```
                 75                  80                  85

GAG TCG GGC CTG GAC ATC AGT CCC ATG TGT GAC AAG CAT ACG GCC TCA
Glu Ser Gly Leu Asp Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser
             90                  95                 100

GTG GAG AAG TCC CAG GTG GGT TTC ATT GAC TAC ATT GCT CAC CCA CTG
Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Ala His Pro Leu
        105                 110                 115

TGG GAG ACT TGG GCT GAC CTG GTC CAC CCA GAT GCA CAG GAC CTG CTG
Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp Ala Gln Asp Leu Leu
    120                 125                 130

GAC ACG CTG GAG GAC AAT CGA GAG TGG TAC CAG AGC AAG ATC CCC CGA
Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr Gln Ser Lys Ile Pro Arg
135                 140                 145                 150

AGT CCC TCA GAC CTC ACC AAC CCC GAG CGG GAC GGG CCT GAC AGA TTC
Ser Pro Ser Asp Leu Thr Asn Pro Glu Arg Asp Gly Pro Asp Arg Phe
                155                 160                 165

CAG TTT GAA CTG ACT CTG GAG GAG GCA GAG GAA GAG GAT GAG GAG GAA
Gln Phe Glu Leu Thr Leu Glu Glu Ala Glu Glu Glu Asp Glu Glu Glu
            170                 175                 180

GAA GAG GAG GGG GAA GAG ACA GCT TTA GCC AAA GAG GCC TTG GAG TTG
Glu Glu Glu Gly Glu Glu Thr Ala Leu Ala Lys Glu Ala Leu Glu Leu
        185                 190                 195

CCT GAC ACT GAA CTC CTG TCC CCT GAA GCC GGC CCA GAC CCT GGG GAC
Pro Asp Thr Glu Leu Leu Ser Pro Glu Ala Gly Pro Asp Pro Gly Asp
    200                 205                 210

TTA CCC CTC GAC AAC CAG AGG ACT TA GGGCCAGCCC TGCGTGAACT
Leu Pro Leu Asp Asn Gln Arg Thr
215                 220

GCAGGGGCAA TGGATGGTAA AGCCCTTTGG CTCTTGGCAG GCAGACTTTC CAGGAAGAGG

CTCCATGTGG CTCCTGCTTC ACTTTCCCAC CCATTTAGGG AGACAATCAA GCTCTTAGTT

ATAGGTGGCT CCCAGGGTCT AATTGGAGGC ACCTGGCTGG GGTCCACTCT GACCCTAGAC

TTGCCTAAAA GAGCTCTCTA AGGGGCAGCC TCTTACGATG CCCTGGTGTC TTTCTCCTGG

GCTTCTATCC CTGTGAGGAG AGGTGCTGTC TGCTGGAGCC TCTAGTCCAC CCTCTCCAGT

GGTCACTCTT GAGTCACATC TGTCACTTAA TTATTTCCTT CTTTATCAAA TATTTATTGC

TCATCTGGAA TTC
```

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 222 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Asn
1 5 10 15

Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser
20 25 30

Leu Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu
35 40 45

Gln Asn Leu Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu
50 55 60

Pro Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Ala Glu Phe Phe Gln
65 70 75 80

Gln Gly Asp Arg Glu Arg Glu Ser Gly Leu Asp Ile Ser Pro Met Cys
85 90 95

Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp
100 105 110

Tyr Ile Ala His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro
115 120 125

Asp Ala Gln Asp Leu Leu Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr
130 135 140

Gln Ser Lys Ile Pro Arg Ser Pro Ser Asp Leu Thr Asn Pro Glu Arg
145 150 155 160

Asp Gly Pro Asp Arg Phe Gln Phe Glu Leu Thr Leu Glu Glu Ala Glu
165 170 175

Glu Glu Asp Glu Glu Glu Glu Glu Glu Gly Glu Glu Thr Ala Leu Ala
180 185 190

Lys Glu Ala Leu Glu Leu Pro Asp Thr Glu Leu Leu Ser Pro Glu Ala
195 200 205

Gly Pro Asp Pro Gly Asp Leu Pro Leu Asp Asn Gln Arg Thr

210 215 220

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Asp Met Val Ile Asp Ile Val
1 5

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Wigler, Michael H.
Colicelli, John J.

(ii) TITLE OF INVENTION: Cloning by Complementation and Related Processes

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Marshall, O'Toole, Gerstein, Murray & Bicknell
(B) STREET: Two First National Plaza, 20 South Clark Street
(C) CITY: Chicago
(D) STATE: Illinois
(E) COUNTRY: USA
(F) ZIP: 60603

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 07/511,715
(B) FILING DATE: 20-APR-1990

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Borun, Michael F.
(B) REGISTRATION NUMBER: 25447
(C) REFERENCE/DOCKET NUMBER: 27805/30197

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (312) 346-5750
(B) TELEFAX: (312) 984-9740
(C) TELEX: 25-3856

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2702 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..2701

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
A AGC TTG CGG CCG CGC GGC CTA GGC CGC ATC CCG GAG CTG CAA CTG
  Ser Leu Arg Pro Arg Gly Leu Gly Arg Ile Pro Glu Leu Gln Leu
   1               5                  10                  15

GTG GCC TTC CCG GTG GCG GTG GCG GCT GAG GAC GAG GCG TTC CTG CCC
Val Ala Phe Pro Val Ala Val Ala Ala Glu Asp Glu Ala Phe Leu Pro
                 20                  25                  30

GAG CCC CTG GCC CCG CGC GCG CCC CGC CGC CGC GTT CGC CGC CCT CCT
Glu Pro Leu Ala Pro Arg Ala Pro Arg Arg Arg Val Arg Arg Pro Pro
             35                  40                  45

CGC CCG TCT TCT TCG CCA GCC CGT CCC CAA CTT TCC GCA GAC GCC TTC
Arg Pro Ser Ser Ser Pro Ala Arg Pro Gln Leu Ser Ala Asp Ala Phe
         50                  55                  60

GGC TTC TCC GCA GCT GCC AGG ATT TGG GCC GCC AGG CTT GGG CTG GGG
Gly Phe Ser Ala Ala Ala Arg Ile Trp Ala Ala Arg Leu Gly Leu Gly
     65                  70                  75

CTG GCT TCG AGG CAG AGA ATG GGC CGA CAC CAT CTC CTG GCC GCA GCC
Leu Ala Ser Arg Gln Arg Met Gly Arg His His Leu Leu Ala Ala Ala
 80                  85                  90                  95

CCT GGA CTG CAG GCG AGC CCA GGA CTC GTG CTG CAC GCC GGG GCG GCC
Pro Gly Leu Gln Ala Ser Pro Gly Leu Val Leu His Ala Gly Ala Ala
                100                 105                 110

ACC AGC CAG CGC CGG GAG TCC TTC CTG TAC CGC TCA GAC AGC GAC TAT
Thr Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr
            115                 120                 125

GAC ATG TCA CCC AAG ACC ATG TCC CGG AAC TCA TCG GTC ACC AGC GAG
Asp Met Ser Pro Lys Thr Met Ser Arg Asn Ser Ser Val Thr Ser Glu
        130                 135                 140
```

GCG CAC GCT GAA GAC CTC ATC GTA ACA CCA TTT GCT CAG GTG CTG GCC
Ala His Ala Glu Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala
145 150 155

AGC CTC CGG AGC GTC CGT AGC AAC TTC TCA CTC CTG ACC AAT GTG CCC
Ser Leu Arg Ser Val Arg Ser Asn Phe Ser Leu Leu Thr Asn Val Pro
160 165 170 175

GTT CCC AGT AAC AAG CGG TCC CCG CTG GGC GGC CCC ACC CCT GTC TGC
Val Pro Ser Asn Lys Arg Ser Pro Leu Gly Gly Pro Thr Pro Val Cys
180 185 190

AAG GCC ACG CTG TCA GAA GAA ACG TGT CAG CAG TTG GCC CGG GAG ACT
Lys Ala Thr Leu Ser Glu Glu Thr Cys Gln Gln Leu Ala Arg Glu Thr
195 200 205

CTG GAG GAG CTG GAC TGG TGT CTG GAG CAG CTG GAG ACC ATG CAG ACC
Leu Glu Glu Leu Asp Trp Cys Leu Glu Gln Leu Glu Thr Met Gln Thr
210 215 220

TAT CGC TCT GTC AGC GAG ATG GCC TCG CAC AAG TTC AAA AGG ATG TTG
Tyr Arg Ser Val Ser Glu Met Ala Ser His Lys Phe Lys Arg Met Leu
225 230 235

AAC CGT GAG CTC ACA CAC CTG TCA GAA ATG AGC AGG TCC GGA AAC CAG
Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln
240 245 250 255

GTC TCA GAG TAC ATT TCC ACA ACA TTC CTG GAC AAA CAG AAT GAA GTG
Val Ser Glu Tyr Ile Ser Thr Thr Phe Leu Asp Lys Gln Asn Glu Val
260 265 270

GAG ATC CCA TCA CCC ACG ATG AAG GAA CGA GAA AAA CAG CAA GCG CCG
Glu Ile Pro Ser Pro Thr Met Lys Glu Arg Glu Lys Gln Gln Ala Pro
275 280 285

CGA CCA AGA CCC TCC CAG CCG CCC CCG CCC CCT GTA CCA CAC TTA CAG
Arg Pro Arg Pro Ser Gln Pro Pro Pro Pro Pro Val Pro His Leu Gln
290 295 300

CCC ATG TCC CAA ATC ACA GGG TTG AAA AAG TTG ATG CAT AGT AAC AGC
Pro Met Ser Gln Ile Thr Gly Leu Lys Lys Leu Met His Ser Asn Ser
305 310 315

CTG AAC AAC TCT AAC ATT CCC CGA TTT GGG GTG AAG ACC GAT CAA GAA
Leu Asn Asn Ser Asn Ile Pro Arg Phe Gly Val Lys Thr Asp Gln Glu
320 325 330 335

GAG CTC CTG GCC CAA GAA CTG GAG AAC CTG AAC AAG TGG GGC CTG AAC
Glu Leu Leu Ala Gln Glu Leu Glu Asn Leu Asn Lys Trp Gly Leu Asn
340 345 350

ATC TTT TGC GTG TCG GAT TAC GCT GGA GGC CGC TCA CTC ACC TGC ATC
Ile Phe Cys Val Ser Asp Tyr Ala Gly Gly Arg Ser Leu Thr Cys Ile
355 360 365

ATG TAC ATG ATA TTC CAG GAG CGG GAC CTG CTG AAG AAA TTC CGC ATC
Met Tyr Met Ile Phe Gln Glu Arg Asp Leu Leu Lys Lys Phe Arg Ile
370 375 380

CCT GTG GAC ACG ATG GTG ACA TAC ATG CTG ACG CTG GAG GAT CAC TAC
Pro Val Asp Thr Met Val Thr Tyr Met Leu Thr Leu Glu Asp His Tyr
385 390 395

CAC GCT GAC GTG GCC TAC CAT AAC AGC CTG CAC GCA GCT GAC GTG CTG
His Ala Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Leu
400 405 410 415

CAG TCC ACC CAC GTA CTG CTG GCC ACG CCT TGG CCA ACC TTA AGG AAT
Gln Ser Thr His Val Leu Leu Ala Thr Pro Trp Pro Thr Leu Arg Asn
420 425 430

GCA GTG TTC ACG GAC CTG GAG ATT CTC GCC GCC CTC TTC GCG GCT GCC
Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Leu Phe Ala Ala Ala
435 440 445

ATC CAC GAT GTG GAT CAC CCT GGG GTC TCC AAC CAG TTC CTC ATC AAC
Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn
450 455 460

ACC AAT TCG GAG CTG GCG CTC ATG TAC AAC GAT GAG TCG GTG CTC GAG
Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu
465 470 475

AAT CAC CAC CTG GCC GTG GGC TTC AAG CTG CTG CAG GAG GAC AAC TGC
Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Asp Asn Cys
480 485 490 495

GAC ATC TTC CAG AAC CTC AGC AAG CGC CAG CGG CAG AGC CTA CGC AAG
Asp Ile Phe Gln Asn Leu Ser Lys Arg Gln Arg Gln Ser Leu Arg Lys
500 505 510

ATG GTC ATC GAC ATG GTG CTG GCC ACG GAC ATG TCC AAG CAC ATG ACC
Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Thr
515 520 525

CTC CTG GCT GAC CTG AAG ACC ATG GTG GAG ACC AAG AAA GTG ACC AGC
Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser
530 535 540

TCA GGG GTC CTC CTG CTA GAT AAC TAC TCC GAC CGC ATC CAG GTC CTC
Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu
545 550 555

CGG AAC ATG GTG CAC TGT GCC GAC CTC AGC AAC CCC ACC AAG CCG CTG
Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu
560 565 570 575

GAG CTG TAC CGC CAG TGG ACA GAC CGC ATC ATG GCC GAG TTC TTC CAG
Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Ala Glu Phe Phe Gln
580 585 590

CAG GGT GAC CGA GAG CGC GAG CGT GGC ATG GAA ATC AGC CCC ATG TGT
Gln Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys
595 600 605

GAC AAG CAC ACT GCC TCC GTG GAG AAG TCT CAG GTG GGT TTT ATT GAC
Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp
610 615 620

TAC ATT GTG CAC CCA TTG TGG GAG ACC TGG GCG GAC CTT GTC CAC CCA
Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro
625 630 635

GAT GCC CAG GAG ATC TTG GAC ACT TTG GAG GAC AAC CGG GAC TGG TAC
Asp Ala Gln Glu Ile Leu Asp Thr Leu Glu Asp Asn Arg Asp Trp Tyr
640 645 650 655

TAC AGC GCC ATC CGG CAG AGC CCA TCT CCG CCA CCC GAG GAG GAG TCA
Tyr Ser Ala Ile Arg Gln Ser Pro Ser Pro Pro Pro Glu Glu Glu Ser
660 665 670

AGG GGG CCA GGC CAC CCA CCC CTG CCT GAC AAG TTC CAG TTT GAG CTG
Arg Gly Pro Gly His Pro Pro Leu Pro Asp Lys Phe Gln Phe Glu Leu
675 680 685

ACG CTG GAG GAG GAA GAG GAG GAA GAA ATA TCA ATG GCC CAG ATA CCG
Thr Leu Glu Glu Glu Glu Glu Glu Glu Ile Ser Met Ala Gln Ile Pro
690 695 700

TGC ACA GCC CAA GAG GCA TTG ACT GAG CAG GGA TTG TCA GGA GTC GAG
Cys Thr Ala Gln Glu Ala Leu Thr Glu Gln Gly Leu Ser Gly Val Glu
705 710 715

GAA GCT CTG GAT GCA ACC ATA GCC TGG GAG GCA TCC CCG GCC CAG GAG
Glu Ala Leu Asp Ala Thr Ile Ala Trp Glu Ala Ser Pro Ala Gln Glu
720 725 730 735

TCG TTG GAA GTT ATG GCA CAG GAA GCA TCC CTG GAG GCC GAG CTG GAG
Ser Leu Glu Val Met Ala Gln Glu Ala Ser Leu Glu Ala Glu Leu Glu
740 745 750

GCA GTG TAT TTG ACA CAG CAG GCA CAG TCC ACA GGC AGT GCA CCT GTG
Ala Val Tyr Leu Thr Gln Gln Ala Gln Ser Thr Gly Ser Ala Pro Val
755 760 765

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GCT CCG GAT GAG TTC TCG TCC CGG GAG GAA TTC GTG GTT GCT GTA AGC
Ala Pro Asp Glu Phe Ser Ser Arg Glu Glu Phe Val Val Ala Val Ser
        770                 775                 780

CAC AGC AGC CCC TCT GCC CTG GCT CTT CAA AGC CCC CTT CTC CCT GCT
His Ser Ser Pro Ser Ala Leu Ala Leu Gln Ser Pro Leu Leu Pro Ala
    785                 790                 795

TGG AGG ACC CTG TCT GTT TCA GAG CAT GCC CGG CCT CCC GGG CCT CCC
Trp Arg Thr Leu Ser Val Ser Glu His Ala Arg Pro Pro Gly Pro Pro
800                 805                 810                 815

CTC CAC GGC GGC CGA GGT GGA GGC CCA ACG AGA GCA CCA GGC TGC CAA
Leu His Gly Gly Arg Gly Gly Gly Pro Thr Arg Ala Pro Gly Cys Gln
                820                 825                 830

GAG GGC TTG CAG TGC CTG CGC AGG GAC ATT TGG GGA GGA CAC ATC CGC
Glu Gly Leu Gln Cys Leu Arg Arg Asp Ile Trp Gly Gly His Ile Arg
            835                 840                 845

ACT CCC AGC TCC TGG TGG CGG GGG GTC AGG TGG AGA CCC TAC CTG ATC
Thr Pro Ser Ser Trp Trp Arg Gly Val Arg Trp Arg Pro Tyr Leu Ile
        850                 855                 860

CCC AGA CCT CTG TCC CTG TTC CCC TCC ACT CCT CCC CTC ACT CCC CTG
Pro Arg Pro Leu Ser Leu Phe Pro Ser Thr Pro Pro Leu Thr Pro Leu
    865                 870                 875

CTC CCC CGA CCA CCT CCT CCT CTG CCT CAA AGA CTC TTG TCC TCT TGT
Leu Pro Arg Pro Pro Pro Pro Leu Pro Gln Arg Leu Leu Ser Ser Cys
880                 885                 890                 895

CCG CGG CCG CAA GCT T
Pro Arg Pro Gln Ala
                900
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 900 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Ser Leu Arg Pro Arg Gly Leu Gly Arg Ile Pro Glu Leu Gln Leu Val
 1               5                  10                  15

Ala Phe Pro Val Ala Val Ala Ala Glu Asp Glu Ala Phe Leu Pro Glu
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20 25 30

Pro Leu Ala Pro Arg Ala Pro Arg Arg Arg Val Arg Arg Pro Pro Arg
35 40 45

Pro Ser Ser Ser Pro Ala Arg Pro Gln Leu Ser Ala Asp Ala Phe Gly
50 55 60

Phe Ser Ala Ala Ala Arg Ile Trp Ala Ala Arg Leu Gly Leu Gly Leu
65 70 75 80

Ala Ser Arg Gln Arg Met Gly Arg His His Leu Leu Ala Ala Ala Pro
85 90 95

Gly Leu Gln Ala Ser Pro Gly Leu Val Leu His Ala Gly Ala Ala Thr
100 105 110

Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp
115 120 125

Met Ser Pro Lys Thr Met Ser Arg Asn Ser Ser Val Thr Ser Glu Ala
130 135 140

His Ala Glu Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser
145 150 155 160

Leu Arg Ser Val Arg Ser Asn Phe Ser Leu Leu Thr Asn Val Pro Val
165 170 175

Pro Ser Asn Lys Arg Ser Pro Leu Gly Gly Pro Thr Pro Val Cys Lys
180 185 190

Ala Thr Leu Ser Glu Glu Thr Cys Gln Gln Leu Ala Arg Glu Thr Leu
195 200 205

Glu Glu Leu Asp Trp Cys Leu Glu Gln Leu Glu Thr Met Gln Thr Tyr
210 215 220

Arg Ser Val Ser Glu Met Ala Ser His Lys Phe Lys Arg Met Leu Asn
225 230 235 240

Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val
245 250 255

Ser Glu Tyr Ile Ser Thr Thr Phe Leu Asp Lys Gln Asn Glu Val Glu
260 265 270

Ile Pro Ser Pro Thr Met Lys Glu Arg Glu Lys Gln Gln Ala Pro Arg
275 280 285

Pro Arg Pro Ser Gln Pro Pro Pro Pro Pro Val Pro His Leu Gln Pro
290 295 300

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Met Ser Gln Ile Thr Gly Leu Lys Lys Leu Met His Ser Asn Ser Leu
305                 310                 315                 320

Asn Asn Ser Asn Ile Pro Arg Phe Gly Val Lys Thr Asp Gln Glu Glu
                325                 330                 335

Leu Leu Ala Gln Glu Leu Glu Asn Leu Asn Lys Trp Gly Leu Asn Ile
            340                 345                 350

Phe Cys Val Ser Asp Tyr Ala Gly Gly Arg Ser Leu Thr Cys Ile Met
        355                 360                 365

Tyr Met Ile Phe Gln Glu Arg Asp Leu Leu Lys Lys Phe Arg Ile Pro
    370                 375                 380

Val Asp Thr Met Val Thr Tyr Met Leu Thr Leu Glu Asp His Tyr His
385                 390                 395                 400

Ala Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Leu Gln
                405                 410                 415

Ser Thr His Val Leu Leu Ala Thr Pro Trp Pro Thr Leu Arg Asn Ala
            420                 425                 430

Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Leu Phe Ala Ala Ala Ile
        435                 440                 445

His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr
    450                 455                 460

Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn
465                 470                 475                 480

His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Asp Asn Cys Asp
                485                 490                 495

Ile Phe Gln Asn Leu Ser Lys Arg Gln Arg Gln Ser Leu Arg Lys Met
            500                 505                 510

Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Thr Leu
        515                 520                 525

Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser
    530                 535                 540

Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Arg
545                 550                 555                 560

Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Glu
                565                 570                 575
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Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Ala Glu Phe Phe Gln Gln
580 585 590

Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp
595 600 605

Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr
610 615 620

Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp
625 630 635 640

Ala Gln Glu Ile Leu Asp Thr Leu Glu Asp Asn Arg Asp Trp Tyr Tyr
645 650 655

Ser Ala Ile Arg Gln Ser Pro Ser Pro Pro Pro Glu Glu Glu Ser Arg
660 665 670

Gly Pro Gly His Pro Pro Leu Pro Asp Lys Phe Gln Phe Glu Leu Thr
675 680 685

Leu Glu Glu Glu Glu Glu Glu Glu Ile Ser Met Ala Gln Ile Pro Cys
690 695 700

Thr Ala Gln Glu Ala Leu Thr Glu Gln Gly Leu Ser Gly Val Glu Glu
705 710 715 720

Ala Leu Asp Ala Thr Ile Ala Trp Glu Ala Ser Pro Ala Gln Glu Ser
725 730 735

Leu Glu Val Met Ala Gln Glu Ala Ser Leu Glu Ala Glu Leu Glu Ala
740 745 750

Val Tyr Leu Thr Gln Gln Ala Gln Ser Thr Gly Ser Ala Pro Val Ala
755 760 765

Pro Asp Glu Phe Ser Ser Arg Glu Glu Phe Val Val Ala Val Ser His
770 775 780

Ser Ser Pro Ser Ala Leu Ala Leu Gln Ser Pro Leu Leu Pro Ala Trp
785 790 795 800

Arg Thr Leu Ser Val Ser Glu His Ala Arg Pro Pro Gly Pro Pro Leu
805 810 815

His Gly Gly Arg Gly Gly Gly Pro Thr Arg Ala Pro Gly Cys Gln Glu
820 825 830

Gly Leu Gln Cys Leu Arg Arg Asp Ile Trp Gly Gly His Ile Arg Thr
835 840 845

Pro Ser Ser Trp Trp Arg Gly Val Arg Trp Arg Pro Tyr Leu Ile Pro

850 855 860

Arg Pro Leu Ser Leu Phe Pro Ser Thr Pro Pro Leu Thr Pro Leu Leu
865 870 875 880

Pro Arg Pro Pro Pro Pro Leu Pro Gln Arg Leu Leu Ser Ser Cys Pro
885 890 895

Arg Pro Gln Ala
900

WHAT IS CLAIMED IS:

1. A method of detecting, in a genetically altered microorganism, a mammalian gene which is capable of modifying a phenotypic alteration associated with the genetic alteration in the microorganism, comprising the steps of:

a) providing mammalian cDNA in an expression vector capable of expressing the mammalian cDNA in the genetically altered microorganism;

b) introducing the expression vector into the genetically altered microorganism, thereby producing genetically altered microorganisms containing the expression vector;

c) maintaining genetically altered microorganisms containing the expression vector under conditions appropriate for growth of said microorganisms; and

d) identifying genetically altered microorganisms in which the phenotypic alteration associated with the genetic alteration in the microorganism is modified.

2. The method according to claim 1 wherein said expression vector comprises a promoter DNA sequence, operatively associated with said mammalian cDNA, said promoter DNA sequence being endogenous to said microorganism.

3. The method according to claim 2 wherein said expression vector is selected from among the group consisting of pADNS, pADANS, pAAUN and pAAUN-ATG.

4. The method according to claim 1 wherein said microorganism is selected from the group consisting of yeast and mammalian cells.

5. The method according to claim 4 wherein said microorganism is a yeast microorganism selected from the group consisting of S. cerevisiae and S. pombe.

6. The method according to claim 5 wherein said microorganism is selected from the group consisting of S. cerevisiae strain TK161-R2V, S. cerevisiae strain 10DAB, S. cerevisiae strain SKN37 and S. pombe strain SP65.

7. The method according to claim 1 wherein said microorganism is a yeast microorganism and said phenotypic alteration is selected from the group consisting of heat shock sensitivity, nitrogen starvation, failure to synthesize normal amounts of glycogen, failure to grow on acetate and failure to sporulate.

8. The method according to claim 1 wherein said genetic alteration in said microorganisms results in the activation, inhibition or attenuation of a cellular reaction in which a cyclic nucleotide phosphodiesterase participates.

9. The method according to claim 1 wherein said genetic alteration is an alteration in a gene encoding a RAS protein.

10. The method according to claim 1 further including isolating said mammalian cDNA from a microorganism identified in step (d).

11. A purified isolated DNA sequence consisting essentially of a DNA sequence encoding a mammalian RAS protein polypeptide and selected from the group consisting of the mammalian cDNA inserts present in plasmids pJC99 (A.T.C.C. 68599), pJC265 (A.T.C.C. 68598), pJC310 (A.T.C.C. 68597), pML5 (A.T.C.C. 68593), pATG16 (A.T.C.C. 68599), and pATG29 (A.T.C.C. 68591).

12. A purified isolated DNA sequence consisting essentially of a DNA sequence encoding an RAS protein polypeptide which DNA sequence hybridizes under stringent hybridization conditions to a DNA sequence according to claim 11.

13. A purified and isolated DNA sequence consisting essentially of a DNA sequence which encodes a polypeptide encoded by a DNA sequence according to claim 11 or 12 by means of degenerate codons.

14. A polypeptide product of the expression in a procaryotic or eucaryotic host cell of a DNA sequence according to claim 11, 12 or 13.

15. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a mammalian cyclic nucleotide phosphodiesterase and selected from the group consisting of the mammalian cDNA inserts present in plasmids pRATDPD (A.T.C.C. 68586), pJC44c (A.T.C.C. 68603), pTM3 (A.T.C.C. 68600), pTM72 (A.T.C.C. 68602), pPDE21 (A.T.C.C.68595), pGB18ARR (A.T.C.C. 68596), pGB25 (A.T.C.C. 68594), and pTM22 (A.T.C.C. 68601).

16. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a mammalian cyclic nucleotide phosphodiesterase which DNA sequence hybridizes under stringent conditions to a DNA sequence selected from the group consisting of DNA sequences according to claim 15 and SEQ ID NOS: 33, 34, 35, 37, and 41.

17. A purified and isolated DNA sequence consisting essentially of a DNA sequence which encodes a polypeptide encoded by a DNA sequence according to claim 15 or 16 by means of degenerate codons.

18. A polypeptide product of the expression in a procaryotic or eucaryotic host cell of a DNA sequence according to claim 15, 16 or 17.

19. A method of identifying a chemical agent which alters the activity of an expression product of a mammalian gene which, when it is expressed in a genetically altered microorganism, modifies a phenotypic alteration associated with a genetic alteration in the microorganism, said method comprising the steps of:

a) expressing the mammalian gene in a genetically altered microorganism, thereby modifying the phenotypic alteration associated with the genetic alteration;

b) contacting the genetically altered microorganism of step (a) with a chemical agent to be assayed, under conditions appropriate for phenotypic assay; and

c) determining whether the phenotypic alteration associated with the genetic alteration modified in step (a) is reversed, wherein reversal of the phenotypic alteration is indicative of a chemical agent which inhibits the mammalian gene.

20. The method according to claim 20 wherein said microorganism is a yeast microorganism.

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jc44x   10     GCCGCGCGGCCTAGGCCGCATCCCGGAGCTGCAACTGGTGGCCTTCCCGGTGGCGGTG
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-     1  gcgGCCGCGCGGCCTAGGCCGCATCCCGGAGCTGCAACTGGTGGCCTTCCCGGTGGCGGTG

jc44x   68  GCGGCTGAGGACGAGGCGTTCCTGCCCGAGCCCCTGGCCCCGCGCGCGCCCCGCCGCCCGC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    62  GCGGCTGAGGACGAGGCGTTCCTGCCCGAGCCCCTGGCCCCGCGCGCGCCCCGCCGCCCGC

jc44x  129  GTTCGCCGCCCTCCTCGCCCGTCTTCTTCGCCAGCCCGTCCCCAACTTTCCGCAGACGCCT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   123  GTTCGCCGCCCTCCTCGCCCGTCTTCTTCGCCAGCCCGTCCCCAACTTTCCGCAGACGCCT

jc44x  190  TCGGCTTCTCCGCAGCTGCCAGGATTTGGGCCGCCAGGgTTGGGCTGGGGCTGGCTTCGAG
            |||||||||||||||||||||||||||||||||||||| ||||||||||||||||||||||
TM3-   184  TCGGCTTCTCCGCAGCTGCCAGGATTTGGGCCGCCAGGcTTGGGCTGGGGCTGGCTTCGAG

jc44x  251  GCAGAGAATGGGCCGACACCATCTCCTGGCCGCAGCCCCCTGGACTCGCAGGCGAGCCCAG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   245  GCAGAGAATGGGCCGACACCATCTCCTGGCCGCAGCCCCCTGGACTCGCAGGCGAGCCCAG

jc44x  312  GACTCGTGCTGCACGCCGGGGCGgCCACCAGCCAGCGCCGGGAGTCCTTCCTGTACCGCTC
            ||||||||||||||||||||||| |||||||||||||||||||||||||||||||||||||
TM3-   306  GACTCGTGCTGCACGCCGGGGCG CCACCAGCCAGCGCCGGGAGTCCTTCCTGTACCGCTC

jc44x  373  AGACAGCGACTATGACATGTCACCCAAGACCATGTCCCGGAACTCATCGGTCACCAGCGAG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   366  AGACAGCGACTATGACATGTCACCCAAGACCATGTCCCGGAACTCATCGGTCACCAGCGAG

jc44x  434  GC
            ||                                                 GCACGCTGAA
                                                               ||||||||||
TM3-   427  GCacagttgcttctctgcggacccctgacctgcctctgtcctcaatcacagGCACGCTGAA

jc44x  446  GACCTCATCGTAACACCATTTGCTCAGGTGCTGGCCAGCCTCCGGAGCGTCCGTAGCAACT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   488  GACCTCATCGTAACACCATTTGCTCAGGTGCTGGCCAGCCTCCGGAGCGTCCGTAGCAACT

jc44x  507  TCTCACTCCTGACCAATGTGCCCGTTCCCAGTAACAAGCGGTCCCccGCTGGGCGGCCCCA
            |||||||||||||||||||||||||||||||||||||||||||||  ||||||||||||||
TM3-   549  TCTCACTCCTGACCAATGTGCCCGTTCCCAGTAACAAGCGGTCCC  GCTGGGCGGCCCCA

jc44x  568  CCCCTGTCTGCAAGGCCACGCTGTC
            |||||||||||||||||||||||||
TM3-   608  CCCCTGTCTGCAAGGCCACGCTGTCagaccttctcagtcactaccctggctgccccttcct

jc44x  593   AGAAGAAACGTGTCAGCAGTTGGCCCGGGAGACTCTGGAGGAGCTGGACTGGTGTCTGGA
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   669  tAGAAGAAACGTGTCAGCAGTTGGCCCGGGAGACTCTGGAGGAGCTGGACTGGTGTCTGGA

jc44x  653  GCAGCTGGAGACCATGCAGACCTATCGCTCTGTCAGCGAGATGGCCTCGCACAAGTTCAAA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   730  GCAGCTGGAGACCATGCAGACCTATCGCTCTGTCAGCGAGATGGCCTCGCACAAGTTCAAA

jc44x  714  AGGATGTTGAACCGTGAGCTCACACACCTGTCAGAAATGAGCAGGTCCGGAAACCAGGTCT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   791  AGGATGTTGAACCGTGAGCTCACACACCTGTCAGAAATGAGCAGGTCCGGAAACCAGGTCT

jc44x  775  CAGAGTACATTTCCACAACATTCCTGGACAAACAGAATGAAGTGGAGATCCCATCACCCAC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   852  CAGAGTACATTTCCACAACATTCCTGGACAAACAGAATGAAGTGGAGATCCCATCACCCAC
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Fig. 1(A)

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jc44x   836 GATGAAGGAACGAGAAAAACAGCAAGCGCCGCGACCAAGACCCTCCCAGCCGCCCCCGCCC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    913 GATGAAGGAACGAGAAAAACAGCAAGCGCCGCGACCAAGACCCTCCCAGCCGCCCCCGCCC

jc44x   897 CCTGTACCACACTTACAGCCCATGTCCCAAATCACAGGGTTGAAAAAGTTGATGCATAGTA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    974 CCTGTACCACACTTACAGCCCATGTCCCAAATCACAGGGTTGAAAAAGTTGATGCATAGTA.

GB14      8                  AACATTCCCCGATTTGGGGTGAAGACCGATCAAGAAGAGCTCCT
                             ||||||||||||||||||||||||||||||||||||||||||||
jc44x   958 ACAGCCTGAACAACTCTAACATTCCCCGATTTGGGGTGAAGACCGATCAAGAAGAGCTCCT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1035 ACAGCCTGAACAACTCTAACATTCCCCGATTTGGGGTGAAGACCGATCAAGAAGAGCTCCT

GB14     52 GGCCCAAGAACTGGAGAACCTGAACAAGTGGGGCCTGAACATCTTTTGCGTGTCGGATTAC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1019 GGCCCAAGAACTGGAGAACCTGAACAAGTGGGGCCTGAACATCTTTTGCGTGTCGGATTAC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1096 GGCCCAAGAACTGGAGAACCTGAACAAGTGGGGCCTGAACATCTTTTGCGTGTCGGATTAC

GB14    113 GCTGGAGGCCGCTCACTCACCTGCATCATGTACATGATATTCCAGGAGCGGGACCTGCTGA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1080 GCTGGAGGCCGCTCACTCACCTGCATCATGTACATGATATTCCAGGAGCGGGACCTGCTGA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1157 GCTGGAGGCCGCTCACTCACCTGCATCATGTACATGATATTCCAGGAGCGGGACCTGCTGA

GB14    174 AGAAATTCCGCATCCCTGTGGACACGATGGTGACATACATGCTGACGCTGGAGGATCACTA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1141 AGAAATTCCGCATCCCTGTGGACACGATGGTGACATACATGCTGACGCTGGAGGATCACTA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1218 AGAAATTCCGCATCCCTGTGGACACGATGGTGACATACATGCTGACGCTGGAGGATCACTA

GB14    235 CCACGCTGACGTGGCCTACCATAACAGCCTGCACGCAGCTGACGTGCTGCAGTCCACCCAC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1202 CCACGCTGACGTGGCCTACCATAACAGCCTGCACGCAGCTGACGTGCTGCAGTCCACCCAC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1279 CCACGCTGACGTGGCCTACCATAACAGCCTGCACGCAGCTGACGTGCTGCAGTCCACCCAC

GB14    296 GTACTGCTGGCCACGCCT         gcActagATGCAGTGTTCACGGACCTGGAGATTC
            ||||||||||||||||||           |    |||||||||||||||||||||||||||
jc44x  1263 GTACTGCTGGCCACGCCTtggccaaccttAaggaATGCAGTGTTCACGGACCTGGAGATTC
            ||||||||||||||||||           |    |||||||||||||||||||||||||||
TM3-   1340 GTACTGCTGGCCACGCCT         gcActagATGCAGTGTTCACGGACCTGGAGATTC

GB14    348 TCGCCGCCCTCTTCGCGGCTGCCATCCACGATGTGGATCACCCTGGGGTCTCCAACCAGTT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1324 TCGCCGCCCTCTTCGCGGCTGCCATCCACGATGTGGATCACCCTGGGGTCTCCAACCAGTT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1392 TCGCCGCCCTCTTCGCGGCTGCCATCCACGATGTGGATCACCCTGGGGTCTCCAACCAGTT

GB14    409 CCTCATCAACACCAATTCGGAGCTGGCGCTCATGTACAACGATGAGTCGGTGCTCGAGAAT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1385 CCTCATCAACACCAATTCGGAGCTGGCGCTCATGTACAACGATGAGTCGGTGCTCGAGAAT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1453 CCTCATCAACACCAATTCGGAGCTGGCGCTCATGTACAACGATGAGTCGGTGCTCGAGAAT

GB14    470 CACCACCTGGCCGTGGGCTTCAAGCTGCTGCAGGAGGACAACTGCGACATCTTCCAGAACC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
jc44x  1446 CACCACCTGGCCGTGGGCTTCAAGCTGCTGCAGGAGGACAACTGCGACATCTTCCAGAACC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   1514 CACCACCTGGCCGTGGGCTTCAAGCTGCTGCAGGAGGACAACTGCGACATCTTCCAGAACC
```

Fig. 1(B)

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GB14     531  TCAGCAAGCGCCAGCGGCAGAGC TACGCAAGATGGTCATCG
              ||||||||||||||||||||||| ||||||||||||||||||
jc44x   1507  TCAGCAAGCGCCAGCGGCAGAGCCTACGCAAGATGGTCATCGACATGGTGCTGGCCACGGA
              ||||||||||||||| |||||||||||||||||||||||||||||||||||||||||||||
TM3-    1575  TCAGCAAGCGCCAGC GCAGAGCCTACGCAAGATGGTCATCGACATGGTGCTGGCCACGGA

jc44x   1568  CATGTCCAAGCACATGACCCTCCTGGCTGACCTGAAGACCATGGTGGAGACCAAGAAAGTG
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1635  CATGTCCAAGCACATGACCCTCCTGGCTGACCTGAAGACCATGGTGGAGACCAAGAAAGTG

jc44x   1629  ACCAGCTCAGGGGTCCTCCTGCTAGATAACTACTCCGACCGCATCCAGGTCCTCCGGAACA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1696  ACCAGCTCAGGGGTCCTCCTGCTAGATAACTACTCCGACCGCATCCAGGTCCTCCGGAACA
                                                                          |||
GB18ARR    1                                                              ACA

jc44x   1690  TGGTGCACTGTGCCGACCTCAGCAACCCCACCAAGCCGCTGGAGCTGTACCGCCAGTGGAC
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1757  TGGTGCACTGTGCCGACCTCAGCAACCCCACCAAGCCGCTGGAGCTGTACCGCCAGTGGAC
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR    4  TGGTGCACTGTGCCGACCTCAGCAACCCCACCAAGCCGCTGGAGCTGTACCGCCAGTGGAC

jc44x   1751  AGACCGCATCATGGCCGAGTTCTTCCAGCAGGGTGACCGAGAGCGCGAGCGTGGCATGGAA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1818  AGACCGCATCATGGCCGAGTTCTTCCAGCAGGGTGACCGAGAGCGCGAGCGTGGCATGGAA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR   65  AGACCGCATCATGGCCGAGTTCTTCCAGCAGGGTGACCGAGAGCGCGAGCGTGGCATGGAA

jc44x   1812  ATCAGCCCCATGTGTGACAAGCACACTGCCTCCGTGGAGAAGTCTCAGGTGGGTTTTATTG
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1879  ATCAGCCCCATGTGTGACAAGCACACTGCCTCCGTGGAGAAGTCTCAGGTGGGTTTTATTG
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR  126  ATCAGCCCCATGTGTGACAAGCACACTGCCTCCGTGGAGAAGTCTCAGGTGGGTTTTATTG

jc44x   1873  ACTACATTGTGCACCCATTGTGGGAGACCTGGGCGGACCTTGTCCACCCAGATGCCCAGGA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    1940  ACTACATTGTGCACCCATTGTGGGAGACCTGGGCGGACCTTGTCCACCCAGATGCCCAGGA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR  187  ACTACATTGTGCACCCATTGTGGGAGACCTGGGCGGACCTTGTCCACCCAGATGCCCAGGA

jc44x   1934  GATCTTGGACACTTTGGAGGACAACCGGGACTGGTACTACAGCGCCATCCGGCAGAGCCCA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    2001  GATCTTGGACACTTTGGAGGACAACCGGGACTGGTACTACAGCGCCATCCGGCAGAGCCCA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR  248  GATCTTGGACACTTTGGAGGACAACCGGGACTGGTACTACAGCGCCATCCGGCAGAGCCCA

jc44x   1995  TCTCCGCCACCCGAGGAGGAGTCAAGGGGGCCAGGCCACCCACCCCTGCCTGACAAGTTCC
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    2062  TCTCCGCCACCCGAGGAGGAGTCAAGGGGGCCAGGCCACCCACCCCTGCCTGACAAGTTCC
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR  309  TCTCCGCCACCCGAGGAGGAGTCAAGGGGGCCAGGCCACCCACCCCTGCCTGACAAGTTCC

jc44x   2056  AGTTTGAGCTGACGCTGGAGGAGGAAGAGGAGGAAGAAATATCAATGGCCCAGATACCGTG
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    2123  AGTTTGAGCTGACGCTGGAGGAGGAAGAGGAGGAAGAAATATCAATGGCCCAGATACCGTG
              |||||||  ||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR  370  AGTTTGAcgTGACGCTGGAGGAGGAAGAGGAGGAAGAAATATCAATGGCCCAGATACCGTG

jc44x   2117  CACAGCCCAAGAGGCATTGACTGAGCAGGGATTGTCAGGAGTCGAGGAAGCTCTGGATGCA
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-    2184  CACAGCCCAAGAGGCATTGACTGAGCAGGGATTGTCAGGAGTCGAGGAAGCTCTGGATGCA
              ||||||||||||||||||||||| |||||||||||||||||||||||||||||||||||||
GB18ARR  431  CACAGCCCAAGAGGCATTGACTGcGCAGGGATTGTCAGGAGTCGAGGAAGCTCTGGATGCA
```

Fig. 1(C)

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jc44x  2178 ACCATAGCCTGGGAGGCATCCCCGGCCCAGGAGTCGTTGGAAGTTATGGCACAGGAAGCAT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2245 ACCATAGCCTGGGAGGCATCCCCGGCCCAGGAGTCGTTGGAAGTTATGGCACAGGAAGCAT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 492 ACCATAGCCTGGGAGGCATCCCCGGCCCAGGAGTCGTTGGAAGTTATGGCACAGGAAGCAT

jc44x  2239 CCCTGGAGGCCGAGCTGGAGGCAGTGTATTTGACACAGCAGGCACAGTCCACAGGCAGTGC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2306 CCCTGGAGGCCGAGCTGGAGGCAGTGTATTTGACACAGCAGGCACAGTCCACAGGCAGTGC
            |||||||||||||||||||||||| ||||||||||||||||||||||||||||||||||||
GB18ARR 553 CCCTGGAGGCCGAGCTGGAGGCAGnGTATTTGACACAGCAGGCACAGTCCACAGGCAGTGC

jc44x  2300 ACCTGTGGCTCCGGATGAGTTCTCGTCCCGGGAGGAATTCGTGGTTGCTGTAAGCCACAGC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2367 ACCTGTGGCTCCGGATGAGTTCTCGTCCCGGGAGGAATTCGTGGTTGCTGTAAGCCACAGC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 614 ACCTGTGGCTCCGGATGAGTTCTCGTCCCGGGAGGAATTCGTGGTTGCTGTAAGCCACAGC

jc44x  2361 AGCCCCTCTGCCCTGGCTCTTCAAAGCCCCCTTCTCCCTGCTTGGAGGACCCTGTCTGTTT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2428 AGCCCCTCTGCCCTGGCTCTTCAAAGCCCCCTTCTCCCTGCTTGGAGGACCCTGTCTGTTT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 675 AGCCCCTCTGCCCTGGCTCTTCAAAGCCCCCTTCTCCCTGCTTGGAGGACCCTGTCTGTTT

jc44x  2422 CAGAGCATGCCC  GGCCTCCCGGGCCTCCCCTCCACGGCGGCCGAGGTGGAGGCCCAACG
            ||||||||||||  |||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2489 CAGAGCATGCCCcgGGCCTCCCGGGCCTCCCCTCCACGGCGGCCGAGGTGGAGGCCCAACG
            |||||||||||||||||||||||| ||||||||||||||||||| ||||||       ||||
GB18ARR 736 CAGAGCATGCCCCGGGCCTCCCGG CCTCCCCTCCACGGCGGCCtAGGTGG       AACG

jc44x  2481 AGAGCACCAGGCTGCCAAGAGGGCTTGCAGTGCCTGCGCAGGGACATTTGGGGAGGACACA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2550 AGAGCACCAGGCTGCCAAGAGGGCTTGCAGTGCCTGCGCAGGGACATTTGGGGAGGACACA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 790 AGAGCACCAGGCTGCCAAGAGGGCTTGCAGTGCCTGCGCAGGGACATTTGGGGAGGACACA

jc44x  2542 TCCGCACTCCCAGCTCCTGGTGGCGGGGGGTCAGGTGGAGACCCTACCTGATCCCCAGACC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2611 TCCGCACTCCCAGCTCCTGGTGGCGGGGGGTCAGGTGGAGACCCTACCTGATCCCCAGACC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 851 TCCGCACTCCCAGCTCCTGGTGGCGGGGGGTCAGGTGGAGACCCTACCTGATCCCCAGACC

jc44x  2603 TCTGTCCCTGTTCCCCTCCACTCCTCCCCTCACTCCCCTGCTCCCCCGACCACCTCCTCCT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM3-   2672 TCTGTCCCTGTTCCCCTCCACTCCTCCCCTCACTCCCCTGCTCCCCCGACCACCTCCTCCT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB18ARR 912 TCTGTCCCTGTTCCCCTCCACTCCTCCCCTCACTCCCCTGCTCCCCCGACCACCTCCTCCT

jc44x  2664 CTGCCTCAAAGACTCTTGTCCTCTTGTCC
            |||||||||||||||||||||||||||||
TM3-   2733 CTGCCTCAAAGACTCTTGTCCTCTTGTCCctcctgagatttttttttttttttttttttt
            ||||||||||||||||||||||||||||||||||||||
GB18ARR 973 CTGCCTCAAAGACTCTTGTCCTCTTGTCCCTCCTGAGA
```

Fig. 1(D)

```
PDE2RR    1                                gaattCcTTCTGACGTGGCATATCACAACA
                                                | |||||||||||||||||||||||
TM72   1300 tttataacctacatgatgactttagaagaccattacCaTTCTGACGTGGCATATCACAACA

PDE2RR   31 GCCTGCACtGCTGCTGATGTAGCCCAGTCGACCCATGTnCTCC TTCTACnCCAGCATTAG
            |||||||| ||||||||||||||||||||||||||||| |||| |||||| ||||||||||
TM72   1361 GCCTGCAC GCTGCTGATGTAGCCCAGTCGACCCATGTtCTCCtTTCTACaCCAGCATTAG

PDE2RR   91 ACGCTGTCTTCACAGATTTGGAaATCCTGGCTGCCATTTTTGCAGCTGCCATCCATGACGT
            |||||||||||||||||||||| ||||||||||||||||||||||||||||||||||||||
TM72   1422 ACGCTGTCTTCACAGATTTGGAgATCCTGGCTGCCATTTTTGCAGCTGCCATCCATGACGT

PDE2RR  152 TGATCATCCTGGAGTCTCCAATCAGTTTCTCATCAACACAAATTCAGAACTTGCTTTGATG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1483 TGATCATCCTGGAGTCTCCAATCAGTTTCTCATCAACACAAATTCAGAACTTGCTTTGATG

PDE2RR  213 TATAATGATGAATCTGTGTTGGAAAATCATCACCTTGCTGTGGGTTTCAAACTGCTGCAAG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1544 TATAATGATGAATCTGTGTTGGAAAATCATCACCTTGCTGTGGGTTTCAAACTGCTGCAAG

PDE2RR  274 AAGAACACTGTGACATCTTCATGAATCTCACCAAGAAGCAGCGTCAGACACTCAGGAAGAT
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1605 AAGAACACTGTGACATCTTCATGAATCTCACCAAGAAGCAGCGTCAGACACTCAGGAAGAT

PDE2RR  335 GGTTATTGACATGGTGTTAGCAACTGATATGTCTAAACATATGAGCCTGCTGGCAGACCTG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1666 GGTTATTGACATGGTGTTAGCAACTGATATGTCTAAACATATGAGCCTGCTGGCAGACCTG

PDE2RR  396 AAGACAATGGTAGAAACGAAGAAAGTTACAAGTTCAGGCGTTCTTCTCCTAGACAACTATA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1727 AAGACAATGGTAGAAACGAAGAAAGTTACAAGTTCAGGCGTTCTTCTCCTAGACAACTATA

PDE2RR  457 CCGATCGCATTCAGGTCCTTCGCAACATGGTACACTGTGCAGACCTGAGCAACCCCACCAA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1788 CCGATCGCATTCAGGTCCTTCGCAACATGGTACACTGTGCAGACCTGAGCAACCCCACCAA

PDE2RR  518 GTCCTTGGAATTGTATCGGCAATGGACAGACCGCATCATGGAGGAATTTTTCCAGCAGGGA
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1849 GTCCTTGGAATTGTATCGGCAATGGACAGACCGCATCATGGAGGAATTTTTCCAGCAGGGA

PDE2RR  579 GACAAAGAGCGGGAGAGGGGAATGGAAATTAGCCCAATGTGTGATAAACACACAGCTTCTG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1910 GACAAAGAGCGGGAGAGGGGAATGGAAATTAGCCCAATGTGTGATAAACACACAGCTTCTG

PDE2RR  640 TGGAAAAAATCCCAGGTTGGTTTCATCGACTACATTGTCCATCCATTGTGGGAGACATGGGC
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   1971 TGGAAAAAATCCCAGGTTGGTTTCATCGACTACATTGTCCATCCATTGTGGGAGACATGGGC

PDE2RR  701 AGATTTGGTACAGCCTGATGCTCAGGACATTCTCGATACCTTAGAAGATAACAGGAACTGG
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   2032 AGATTTGGTACAGCCTGATGCTCAGGACATTCTCGATACCTTAGAAGATAACAGGAACTGG

PDE2RR  762 TATCAGAGCATGATACCTCAAAGTCCCTCACCACCACTGGACGAGCAGAACAGGGACTGCC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   2093 TATCAGAGCATGATACCTCAAAGTCCCTCACCACCACTGGACGAGCAGAACAGGGACTGCC

PDE2RR  823 AGGGTCTGATGGAGAAGTTTCAGTTTGAACTGACTCTCGATGAGGAAGATTCTGAAGGACC
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72   2154 AGGGTCTGATGGAGAAGTTTCAGTTTGAACTGACTCTCGATGAGGAAGATTCTGAAGGACC
```

Fig. 2(A)

```
PDE2RR       884 TGAGAAGGAGGGAGAGGGACACAGCTATTTCAGCAGCACAAAGACGCTTTGTGTGATTGAT
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2215 TGAGAAGGAGGGAGAGGGACACAGCTATTTCAGCAGCACAAAGACGCTTTGTGTGATTGAT

PDE2RR       945 CCAGAAAACAGAGATTCCCTGGGAGAGACTGACATAGACATTGCAACAGAAGACAAGTCCC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2276 CCAGAAAACAGAGATTCCCTGGGAGAGACTGACATAGACATTGCAACAGAAGACAAGTCCC

PDE2RR      1006 CCGTGGATACATAATCCCCCTCTCCCTGTGGAGATGAACATTCTATCCTTGATGAGCATGC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2337 CCGTGGATACATAATCCCCCTCTCCCTGTGGAGATGAACATTCTATCCTTGATGAGCATGC

PDE2RR      1067 CAGCTATGTGGTAGGGCCAGCCCACCATGGGGGCCAAGACCTGCACAGGACAAGGGCCACC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2337 CAGCTATGTGGTAGGGCCAGCCCACCATGGGGGCCAAGACCTGCACAGGACAAGGGCCACC
                                     |||||||||||||||||||||||||||||||||||||||||
PDE7          20                     CCCACCATGGGGGCCAAGACCTGCACAGGACAAgGGCCACC
                                     ||||||||||||||||||||||||||||||||| |||||||
PDE10X-INV     7                     CCCACCATGGGGGCCAAGACCTGCACAGGACAA GGCCACC

PDE2RR      1128 TGGCCTTTCAGTTACTTGAGTTTGGAGTCAGAAAGCAAGACCAGGAAGCAAATAGCAGCTC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2398 TGGCCTTTCAGTTACTTGAGTTTGGAGTCAGAAAGCAAGACCAGGAAGCAAATAGCAGCTC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE7          62 TGGCCTTTCAGTTACTTGAGTTTGGAGTCAGAAAGCAAGACCAGGAAGCAAATAGCAGCTC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV    48 TGGCCTTTCAGTTACTTGAGTTTGGAGTCAGAAAGCAAGACCAGGAAGCAAATAGCAGCTC

PDE2RR      1189 AGGAAATCCCACGGTTGACTTGCCTTGATGGCAAGCTTGGTGGAGAGGGCTGAAGCTGTTG
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2459 AGGAAATCCCACGGTTGACTTGCCTTGATGGCAAGCTTGGTGGAGAGGGCTGAAGCTGTTG
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE7         123 AGGAAATCCCACGGTTGACTTGCCTTGATGGCAAGCTTGGTGGAGAGGGCTGAAGCTGTTG
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV   109 AGGAAATCCCACGGTTGACTTGCCTTGATGGCAAGCTTGGTGGAGAGGGCTGAAGCTGTTG

PDE2RR      1250 CTGGGGGCCGATTCTGATCAAGACACATGGCTTGAAAATGGAAGACACAAAACcGAGAGAT
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||| |||||||
TM72        2520 CTGGGGGCCGATTCTGATCAAGACACATGGCTTGAAAATGGAAGACACAAAACtGAGAGAT
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE7         184 CTGGGGGCCGaTTCTGATCAAGACACATGGCTTGAAAATGGAAGACACAAAACTGAGAGAT
                 |||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV   170 CTGGGGGCCGnTTCTGATCAAGACACATGGCTTGAAAATGGAAGACACAAAACTGAGAGAT

PDE2RR      1311 CATTCTGCACTAAGTTTCGGGAACTTATCCCCGACAGTGACTGAACTCACTGACTAATAAC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
TM72        2581 CATTCTGCACTAAGTTTCGGGAACTTATCCCCGACAGTGACTGAACTCACTGACTAATAAC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE7         245 CATTCTGCACTAAGTTTCGGGAACTTATCCCCGACAGTGACTGAACTCACTGACTAATAAC
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV   231 CATTCTGCACTAAGTTTCGGGAACTTATCCCCGACAGTGACTGAACTCACTGACTAATAAC

PDE2RR      1372 TTCATTTATGAATCTTCTCcCTTGTCCCTTTGTCTGCCAACCTGTGTGCCTTTTTTGTAAA
                 ||||||||||||||||||| |||||||||||||||||||||||||||||||||||||||||
TM72        2642 TTCATTTATGAATCTTCTCaCTTGTCCCTTTGTCTGCCAACCTGTGTGCCTTTTTTGTAAA

PDE7         306 TTCATTTATGAATCTTCTCCCTTGTCCCTTTGTCTGCCAACCTGTGTGCCTTTTTTGTAAA
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV   292 TTCATTTATGAATCTTCTCCCTTGTCCCTTTGTCTGCCAACCTGTGTGCCTTTTTTGTAAA
```

Fig. 2(B)

```
    PDE2RR 1433 ACATTTTCATGTCTTTAAAATGCCTGTTGAATACCTGGAGTTTAGTATCAACTTCTACACA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      TM72 2703 ACATTTTCATGTCTTTAAAATGCCTGTTGAATACCTGGAGTTTAGTATCAACTTCTACACA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  367 ACATtTTCAtGTCTTTAAAATGCCTGTTGAATACCTGGAGTTtagtATCAACTTCTACACA
                |||| |||| ||||||||||||||||||||||||||||||||    |||||||||||||||
PDE10X-INV  353 ACATnTTCAnGTCTTTAAAATGCCTGTTGAATACCTGGAGTT  agATCAACTTCTACACA

    PDE2RR 1494 GATAAGCTTTCAAAGTTGACAAACTTTTTTGACTCTTTCTGGAAAAGGGAAAGAAAATAGT
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      TM72 2764 GATAAGCTTTCAAAGTTGACAAACTTTTTTGACTCTTTCTGGAAAAGGGAAAGAAAATAGT
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  428 GATAAGCTTTCAAAGTTGACAAACTTTTTTGACTCTTtCTGGAAAAGGGAAAGAAAATAGT
                ||||||||||||||||||||||||||||||||||||| |||||||||||||||||||||||
PDE10X-INV  412 GATAAGCTTTCAAAGTTGACAAACTTTTTTGACTCTT CTGGAAAAGGGAAAGAAAATAGT

    PDE2RR 1555 CTTCCTTCTTTCTTGGGCAATATCCTTCACTTTACTACAGTTACTTTTGCAAACAGACAGA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      TM72 2825 CTTCCTTCTTTCTTGGGCAATATCCTTCACTTTACTACAGTTACTTTTGCAAACAGACAGA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  488 CTTCCTTCTTTCTTGGGCAATATCCTTCACTTTACTACAGTTACTTTTGCAAACAGACAGA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  471 CTTCCTTCTTTCTTGGGCAATATCCTTCACTTTACTACAGTTACTTTTGCAAACAGACAGA

    PDE2RR 1616 AAGGATACACTTCTAACCACATTTTAC
                |||||||||||||||||||||||||||
      TM72 2886 AAGGATACACTTCTAACCACATTTTACttccttcccctgttgtccagtccaactccacagt
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  549 AAGGATACACTTCTAACCACATTTTACTTCCTTCCCCTGTTGTCCAGTCCAACTCCACAGT
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  532 AAGGATACACTTCTAACCACATTTTACTTCCTTCCCCTGTTGTCCAGTCCAACTCCACAGT

      TM72 2947 cactcttaaaacttctctctgtttgcctgcctccaacagt       acttttaacttttt
                ||||||||||||||||||||||||||||||||||||||||       ||||||||||||||
      PDE7  610 CACTCTTAAAACTTCTCTCTGTTTGCCTGCCTCCAACAGT       ACTTTTAACTTTTT
                ||||||||||||||||||||||||||||||||||||||||       ||||||||||||||
PDE10X-INV  593 CACTCTTAAAACTTCTCTCTGTTTGCCTGCCTCCAACAGTACTTTTAACTTTTAACTTTTT

      TM72  662 GCTGTAAACAGAATAAAATTGAACAAATTAGGGGGTAGAAAGGAGCAGTGGTGTCGTTCAC
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  664 GCTGTAAACAGAATAAAATTGAACAAATTAGGGGGTAGAAAGGAGCAGTGGTGTCGTTCAC
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  654 GCTGTAAACAGAATAAAATTGAACAAATTAGGGGGTAGAAAGGAGCAGTGGTGTCGTTCAC

      TM72  723 CGTGAGAGTCTGCATAGAACTCAGCAGTGTGCCCTGCTGTGTCTTGGACCCTGC
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||
      PDE7  725 CGTGAGAGTCTGCATAGAACTCAGCAGTGTGCCCTGCTGTGTCTTGGACCCTGCCCCCCAC
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  715 CGTGAGAGTCTGCATAGAACTCAGCAGTGTGCCCTGCTGTGTCTTGGACCCTGCCCCCCAC

      PDE7  786 AGGAGTTGTACAGTCCCTGGCCCTGTTCCCTACCTCCTCTCTTCACCCCGTTAGGCTGTTT
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  776 AGGAGTTGTACAGTCCCTGGCCCTGTTCCCTACCTCCTCTCTTCACCCCGTTAGGCTGTTT

      PDE7  847 TCAATGTAATGCTGCCGTCCTTCTCTTGCACTGCCTTCTGCGCTAACACCTCCATTCCTGT
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  837 TCAATGTAATGCTGCCGTCCTTCTCTTGCACTGCCTTCTGCGCTAACACCTCCATTCCTGT

      PDE7  908 TTATAACCGTGTATTTATTACTTAATGTATATAATGTAATGTTTTGTAAGTTATTAATTTA
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  898 TTATAACCGTGTATTTATTACTTAATGTATATAATGTAATGTTTTGTAAGTTATTAATTTA
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Fig. 2(C)

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PDE7         969  TATATCTAACATTGCCTGCCAATGGTGGTGTTAAATTTGTGTAGAAAACTCTGCCTAAGAG
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV   959  TATATCTAACATTGCCTGCCAATGGTGGTGTTAAATTTGTGTAGAAAACTCTGCCTAAGAG

PDE7        1030  TTACGACTTTTTCTTGTAATGTTTTGTATTGTGTATTATATAACCCAAACGTCACTTAGTA
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1020  TTACGACTTTTTCTTGTAATGTTTTGTATTGTGTATTATATAACCCAAACGTCACTTAGTA

PDE7        1091  GAGACATATGGCCCCCTTGGCAGAGAGGACAGGGGTGGGCTTTTGTTCAAAGGGTCTGCCC
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1081  GAGACATATGGCCCCCTTGGCAGAGAGGACAGGGGTGGGCTTTTGTTCAAAGGGTCTGCCC

PDE7        1152  TTTCCCTGCCTGAGTTGCTACTTCTGCACAACCCCTTTATGAACCAGTTTTGGAAACAATA
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1142  TTTCCCTGCCTGAGTTGCTACTTCTGCACAACCCCTTTATGAACCAGTTTTGGAAACAATA

PDE7        1213  TTCTCACATTAGATACTAAATGGTTTATACTGAGCTTTTACTTTTGTATAGCTTGATAGGG
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1203  TTCTCACATTAGATACTAAATGGTTTATACTGAGCTTTTACTTTTGTATAGCTTGATAGGG

PDE7        1274  GCAGGGGGCAATGGGATGTAGTTTTTACCCAGGTTCTATCCAAATCTATGTGGGCATGAGT
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1264  GCAGGGGGCAATGGGATGTAGTTTTTACCCAGGTTCTATCCAAATCTATGTGGGCATGAGT

PDE7        1335  TGGGTTATAACTGGATCCTACTATCATTGTGGCTTTGGTTCAAAAGGAAACACTACATTTG
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1325  TGGGTTATAACTGGATCCTACTATCATTGTGGCTTTGGTTCAAAAGGAAACACTACATTTG

PDE7        1396  CTCACAGATGATTCTTCTGAATGCTCCCGAACTACTGACTTTGAAGAGGTAGCCTCCTGCC
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1386  CTCACAGATGATTCTTCTGAATGCTCCCGAACTACTGACTTTGAAGAGGTAGCCTCCTGCC

PDE7        1457  TGCCATTAAGCAGGAATGTCATGTTCCAGTTCATTACAAAAGAAAACAATAAAACAATGTG
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1447  TGCCATTAAGCAGGAATGTCATGTTCCAGTTCATTACAAAAGAAAACAATAAAACAATGTG

PDE7        1518  AATTTTTATAATAAAATGTGAACTGATGTAGCAAATTACGCAAATGTGAAGCCTCTTCTGA
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1508  AATTTTTATAATAAAATGTGAACTGATGTAGCAAATTACGCAAATGTGAAGCCTCTTCTGA

PDE7        1579  TAACACTTGTTAGGCCTCTTACTGATGTCAGTTTCAGTTTGTAAAATATGTTTCATGCTTT
                  |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
PDE10X-INV  1569  TAACACTTGTTAGGCCTCTTACTGATGTCAGTTTCAGTTTGTAAAATATGTTTCATGCTTT

PDE7        1640  CAGTTCAGCATTGTGACTCAGTAATTACAGAAAAtggcacaaatgtgcatgaccaatgggt
                  ||||||||||||||||||||||||||||||||||
PDE10X-INV  1630  CAGTTCAGCATTGTGACTCAGTAATTACAGAAAA
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Fig. 2(D)

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PDE18    1 GAATTCCT      TtgTTCA
           ||||||||      |  ||||                                   catcttctAgtT
GB25     1 GAATTCCTctgacTaaTTCAagtatcccaaggtttggagttaaaactgaacaagaagAtgT

PDE18   28 CCTTGgCAAGGA                             caTCTTCATGTTTTCAGAATAGCAGAG
           ||||| ||||||                               |||||||||||||||||||||||||
GB25    62 CCTTGcCAAGGAactagaagatgtgaacaaatggggTCTTCATGTTTTCAGAATAGCAGAG

PDE18   67 TTGTCTGGTAACCGGCCCTTGACTGTTATCATGCACACCATTTTTCAGGAACGGGATTTAT
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   123 TTGTCTGGTAACCGGCCCTTGACTGTTATCATGCACACCATTTTTCAGGAACGGGATTTAT

PDE18  128 TAAAAACATTTAAAATTCCAGTAGATACTTTAATTACATATCTTATGACTCTCGAAGACCA
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   184 TAAAAACATTTAAAATTCCAGTAGATACTTTAATTACATATCTTATGACTCTCGAAGACCA

PDE18  189 TTACCATGCTGATGTGGCCTATCACAACAATATCCATGCTGCAGATGTTGTCCAGTCTACT
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   245 TTACCATGCTGATGTGGCCTATCACAACAATATCCATGCTGCAGATGTTGTCCAGTCTACT

PDE18  250 CATGTGCTATTATCTACACCTGCTTTGGAGGCTGTGTTTACAGATTTGGAGATTCTTGCAG
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   306 CATGTGCTATTATCTACACCTGCTTTGGAGGCTGTGTTTACAGATTTGGAGATTCTTGCAG

PDE18  311 CAATTTTTGCCAGTGCAATACATGATGTAGATCATCCTGGTGTGTCCAATCAATTTCTGAT
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   367 CAATTTTTGCCAGTGCAATACATGATGTAGATCATCCTGGTGTGTCCAATCAATTTCTGAT

PDE18  372 CAATACAAACTCTGAACTTGCCTTGATGTACAATGATTCCTCAGTCTTAGAGAACCATCAT
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   428 CAATACAAACTCTGAACTTGCCTTGATGTACAATGATTCCTCAGTCTTAGAGAACCATCAT

PDE18  433 TTGGCTGTGGGCTTTAAATTGCTTCAGGAAGAAAACTGTGACATTTTCCAGAATTTGACCA
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   489 TTGGCTGTGGGCTTTAAATTGCTTCAGGAAGAAAACTGTGACATTTTCCAGAATTTGACCA

PDE18  494 AAAAACAAAGACAATCTTTAAGGAAAATGGTCATTGACATCGTACTTGCAACAGATATGTC
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   550 AAAAACAAAGACAATCTTTAAGGAAAATGGTCATTGACATCGTACTTGCAACAGATATGTC

PDE18  555 AAAACACATGAATCTACTGGCTGATTTGAAGACTATGGTTGAAACTAAGAAAGTGACAAGC
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   611 AAAACACATGAATCTACTGGCTGATTTGAAGACTATGGTTGAAACTAAGAAAGTGACAAGC

PDE18  616 TCTGGAGTTCTTCTTCTTGATAATTATTCCGATAGGATTCAGGTTCTTCAGAATATGGTGC
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   672 TCTGGAGTTCTTCTTCTTGATAATTATTCCGATAGGATTCAGGTTCTTCAGAATATGGTGC

PDE18  677 ACTGTGCAGATCTGAGCAACCCAACAAAGCCTCTCCAGCTGTACCGCCAGTGGACGGACcg
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
GB25   733 ACTGTGCAGATCTGAGCAACCCAACAAAGCCTCTCCAGCTGTACCGCCAGTGGACGGAC
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Fig. 3

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TM72     212                                                                SLRsVRNNFTiLTNL
RATDPD     1                                                                SLRiVRNNFTlLTNL

TM72     219 HGtsNKRSPAASQpPVsRVnpQEESYQKLAMETLEELDWCLDQLETIQTYRSVSEMASNKF
RATDPD     8 HGapNKRSPAASQaPVtRVSlQEESYQKLAMETLEELDWCLDQLETIQTYRSVSEMASNKF
JC44X     25                      EEtcQqLArETLEELDWCLeQLETmQTYYSVSEMAShKF

TM72     287 KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSPTQKDREK
RATDPD    72 KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSPTQKDREK
JC44X     59 KRMLNRELTHLSEMSRSGNQVSEYIStTFLDKQNeVEIPSPTmKeREKqQaprprPSQppp

TM72     335   KKKQQLMTQISGVKKLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWGLNIFNVAG
RATDPD   124   KKKQQLMTQISGVKKLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWGLNIFNVAG
JC44X    123 ppvphlQpMsQItGlKKLMHSnSLNNsnIpRFGVkTdqEelLAqELEnLNKWGLNIFcVsd

PDE18     25   gNRPLTvIMhtIFQERDLLKTFkIpvDTlITYlMTLEDHYHaDVAYHNniHAADVvQST
TM72     394 YSHNRPLTCIMYAIFQERDLLKTFrISSDTFITYMMTLEDHYHSDVAYHNSLHAADVAQST
RATDPD   183 YSHNRPLTCIMYAIFQERDLLKTFkISSDTFVTYMMTLEDHYHSDVAYHNSLHAADVAQST
JC44X    184 YaggRsLTCIMYmIFQERDLLKkFrIpvDTmVTYMlTLEDHYHaDVAYHNSLHAADVlQST

PDE18     85 HVLLSTP   ALeAVFTDLEILAAIFAsAIHDVDHPGVSNQFLINTNSELALMYNDsSVLE
TM72     455 HVLLSTP   ALDAVFTDLEILAAIFAAAIHDVDHPGVSNQFLINTNSELALMYNDESVLE
RATDPD   244 HVLLSTP   ALDAVFTDLEILAAIFAAAIHDVDHPGVSNQFLINTNSELALMYNDESVLE
JC44X    245 HVLLaTPwptlrnAVFTDLEILAAlFAAAIHDVDHPGVSNQFLINTNSELALMYNDESVLE

PDE21      3    LAVGFKLLQaENCDIFQNLsaKQRlSLRrMVIDmVLATDMSKHMNLLADLKTMVETKK
PDE18    143 NHHLAVGFKLLQEENCDIFQNLTKKQRQSLRKMVIDiVLATDMSKHMNLLADLKTMVETKK
TM72     513 NHHLAVGFKLLQEEHCDIFmNLTKKQRQTLRKMVIDMVLATDMSKHMSLLADLKTMVETKK
RATDPD   302 NHHLAVGFKLLQEEHCDIFQNLTKKQRQTLRKMVIDMVLATDMSKHMSLLADLKTMVETKK
JC44X    306 NHHLAVGFKLLQEdnCDIFQNLsKrQRQsLRKMVIDMVLATDMSKHMtLLADLKTMVETKK

PDE21     61 VTSlGVLLLDNYSDRIQVLQNlVHCADLSNPTKPLpLYRQWTDRIMaEFFqQGDRERESGl
PDE18    204 VTSSGVLLLDNYSDRIQVLQNMVHCADLSNPTKPLqLYRQWTDRIMEEFFrQGDRERERGM
TM72     574 VTSSGVLLLDNYTDRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGM
RATDPD   363 VTSSGVLLLDNYTDRIQVLRNMVHCADLSNPTKSLELYRQWTDRIMEEFFQQGDKERERGM
JC44X    367 VTSSGVLLLDNYsDRIQVLRNMVHCADLSNPTKpLELYRQWTDRIMaEFFQQGDrERERGM
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Fig. 4(A)

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PDE21   122 dISPMCDKHtASVEKSQVGFIDYIaHPLWETWADLVHPDAQDlLDTLEDNREWYQSkIPrS
PDE18   265 EISPMCDKHnASVEKSQVGFIDYIVHPLWETWADLVHPDAQDILDTLEDNREWYQStIPQS
TM72    635 EISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDTLEDNRNWYQSMIPQS
RATDPD  424 EISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVQPDAQDILDTLEDNRNWYQSMIPQS
JC44X   428 EISPMCDKHTASVEKSQVGFIDYIVHPLWETWADLVhPDAQeILDTLEDNRdWYySaIrQS

PDE21   183 PS    DltnPE     rdgpdrFQFELTLEE                aeEEDeeeeeegeetalakE
PDE18   326 PSPapD   dPEegrQGqtEKFQFELTLEEdgesdtEKdsgsqvEEDtscSdsKTLCtqdsE
TM72    696 PSPPLDEqnR   DCQGLMEKFQFELTLdEEDSEGPEK     EGEGhsYFSSTKTLC
RATDPD  485 PSPPLDErSR   DCQGLMEKFQFELTLEEEDSEGPEK     EGEGpnYFSSTKTLC
JC44X   489 PSPPpeEeSRgpghppLpdKFQFELTLEEEeeEeismaqipctaqealteqglsgveeald

PDE21   225 alElPdtEllspEAgpdpgdlpldnqrt
PDE18   386 stEiPldEqveeEAvGEeeesqpeacviDdrspDT
TM72    743       VIDPENRDSLGE      TDIDIATEDKSpvDT
RATDPD  536       VIDPENRDSLeE      TDIDIATEDKSLiDT
JC44X   551 atiaweasPaqeslevmaqeasleaelEavyLtqq
```

Fig. 4(B)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/02714

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C12Q 1/68; C07H 15/12; C07K 3/00
U.S. CL.: 435/6; 536/27; 530/350

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	435/6; 536/27; 530/350

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

APS, GENBANK, EMBL

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	US, A, 4,861,709 (**ULITZUR ET AL.**) 29 August 1989, see claim 1.	1,2 3-10, 19
X Y	Proceedings of the National Academy of Sciences, Vol. 86, issued July 1989, **SWINNEN ET AL.**, "Molecular cloning of rat homologues of the Drosophila melanogaster dunce cAMP phosphodiesterase: Evidence for a family of genes", pages 5325-5329, see especially Figs. 1 and 2.	16-17 18
X Y	Proceedings of the National Acedemy of Sciences, Vol. 86, issued November 1989, **SWINNEN ET AL.**, "The mRNA Encoding a High-Affinity cAMP phosphodiesterase is Regulated by Horomes and cAMP", pages 8197-8201, see especially Fig. 1.	16-17 18
X Y	Journal of Molecular Biology, Vol. 156, issued 1982, **HEILIG ET AL.**, "The Ovalbumin Gene Family", pages 1-19, see entire document.	16-17 18

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 August 1991	21 AUG 1991

International Searching Authority	Signature of Authorized Officer
ISA/US	Mindy B. Fleisher Mindy B. Fleisher (vsh)

Form PCT/ISA/210 (second sheet) (Rev. 11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers__________, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-13 and 15-17 drawn to DNA and method of use classified in Class 435, subclass 6.

II. Claims 14 and 18 drawn to polypeptide classified in Class 530, subclass 350.

III. Claims 19-20 drawn to a method of identifying, classified in class 435, subclass 243.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. **Telephone Practice.**

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.